

AIR FORCE HEALTH STUDY

FINAL REPORT

*An Epidemiologic Investigation of
Health Effects in Air Force Personnel
Following Exposure to Herbicides*

1997 Follow-up Examination Results
May 1997 to February 2000

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NOTICE

This report presents the results of the 1997 follow-up of the Air Force Health Study, the fifth examination in a series of epidemiological studies to investigate the health effects in Air Force personnel following exposure to herbicides. The results of the 1982 baseline study, the 1985 follow-up study, the 1987 follow-up study, and the 1992 follow-up study were presented in five reports: the Baseline Morbidity Study Results (24 February 1987), the Air Force Health Study First Followup Examination Results (15 July 1987), the Air Force Health Study 1987 Followup Examination Results (16 January 1990), the Air Force Health Study Serum Dioxin Analysis of 1987 Examination Results (7 February 1991), and the Air Force Health Study 1992 Followup Examination Results (2 May 1995).

Given the relationship of the 1997 follow-up to the previous studies, portions of these documents have been reproduced or paraphrased in this report. In addition, portions of the Air Force Health Study Statistical Plan for the 1997 follow-up (20 May 1998) have been used in the development of this report. The purpose of this notice is to acknowledge the authors of these previous study reports and documents.

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13. ABSTRACT (Maximum 200 words) This report summarizes results from the Air Force Health Study (AFHS). The AFHS is an epidemiological study to determine whether adverse health effects attributable to exposure to herbicides exist in veterans of Operation Ranch Hand. Operation Ranch Hand was the unit responsible for the aerial spraying of herbicides, including Herbicide Orange, in Vietnam from 1961 to 1971. A Comparison cohort comprised Air Force veterans who served in Southeast Asia during the same time period that the Ranch Hand unit was active and who were not involved with spraying herbicides. The summarized data were collected during a physical examination administered between May 1997 and April 1998. Of 1,149 eligible Ranch Hands, 870 (75.7%) participated and of 1,761 eligible Comparisons, 1,251 (71.0%) participated. Statistical analyses assessed differences between Ranch Hands and Comparisons and associations between health-related endpoints and extrapolated initial dioxin, dioxin exposure category (Comparisons, background Ranch Hands, low Ranch Hands, high Ranch Hands), and dioxin measured in 1987. The study has insufficient statistical power to assess increases in the risk of rare diseases, such as soft tissue sarcoma. Diabetes and cardiovascular abnormalities represent the most important dioxin-related health problems seen. From a public health perspective, these two areas demand the greatest attention.			
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Table of Contents

1 INTRODUCTION	1-1
1.1 PURPOSE OF THE REPORT	1-1
1.2 BACKGROUND	1-1
1.3 STUDY DESIGN	1-2
1.4 MORBIDITY COMPONENT	1-3
1.5 ORGANIZATION OF THE REPORT	1-5
1.6 INTERPRETIVE CONSIDERATIONS	1-6
1.6.1 Study Design and Modeling Considerations	1-6
1.6.2 The Air Force Exposure Index	1-8
1.6.3 Information Bias	1-9
1.6.4 Consistency of Results	1-10
1.6.5 Strength of Association	1-10
1.6.6 Biological Plausibility	1-10
1.6.7 Interpretation of Nonsignificant Results	1-11
1.6.8 Extrapolation to Armed Forces Ground Troops	1-11
1.6.9 Considerations for Summarizing Results	1-11
REFERENCES.....	1-12
2 THE DIOXIN ASSAY	2-1
2.1 PARTICIPANTS SELECTED FOR DIOXIN MEASUREMENT	2-1
2.2 SAMPLE ACQUISITION	2-2
2.3 ANALYTICAL METHOD	2-2
2.4 QUALITY CONTROL.....	2-2
2.5 DATA DESCRIPTION	2-3
2.6 LIPID-ADJUSTED AND WHOLE-WEIGHT CURRENT DIOXIN MEASUREMENTS	2-6
2.7 SUMMARY	2-9
REFERENCES.....	2-10
3 QUESTIONNAIRE METHODOLOGY	3-1
3.1 QUESTIONNAIRE DEVELOPMENT.....	3-1
3.1.1 Baseline Questionnaire	3-1
3.1.2 Interval Questionnaire.....	3-2
3.2 INTERVIEWER TRAINING	3-3
3.3 DATA COLLECTION	3-3
REFERENCES.....	3-5
4 PHYSICAL EXAMINATION METHODOLOGY	4-1
4.1 EXAMINATION CONTENT	4-1

4.2	ADIPOSE TISSUE EXTRACTION	4-4
4.3	QUALITY CONTROL.....	4-4
4.4	CONDUCT OF EXAMINATIONS	4-5
4.4.1	Blood Collection.....	4-5
5	STUDY SELECTION AND PARTICIPATION.....	5-1
5.1	INTRODUCTION	5-1
5.2	FACTORS KNOWN OR SUSPECTED TO INFLUENCE STUDY PARTICIPATION	5-1
5.3	REPLACEMENT PROTOCOL.....	5-2
5.4	1997 FOLLOW-UP SCHEDULING AND REPLACEMENT OPERATION.....	5-3
5.4.1	Scheduling Strategy	5-3
5.4.2	Replacement Strategy	5-4
5.5	COMPLIANCE	5-6
5.5.1	Corrections to Previously Reported Study Compliance Totals	5-8
5.5.2	Analysis of Refusals	5-10
5.5.2.1	Passive Refusals.....	5-12
5.5.2.2	Hostile Refusals	5-12
5.5.2.3	Reasons for Refusal Across AFHS Examinations.....	5-12
5.5.3	Replacement Comparisons	5-14
5.6	MATCHING OF SELF-REPORTED HEALTH STATUS	5-15
5.6.1	Self-reported Health Status of Refusals	5-15
5.6.2	Self-reported Health Status of Fully Compliant Participants	5-17
5.7	CONCLUSION.....	5-19
REFERENCE.....		5-20
6	QUALITY CONTROL	6-1
6.1	QUESTIONNAIRE QC.....	6-1
6.1.1	Design	6-1
6.1.2	Data Collection	6-2
6.1.3	Processing and QA of Questionnaire Data	6-2
6.2	PHYSICAL EXAMINATION QC.....	6-4
6.3	LABORATORY QC	6-5
6.3.1	QC Procedures for the Clinical Laboratory	6-6
6.4	MEDICAL DATA QC	6-7
6.4.1	Overview of QC Procedures	6-7
6.4.2	Data Processing System Design.....	6-8
6.4.3	Design and Administration of Physical and Psychological Examination Forms	6-9
6.4.4	Data Completeness Checks	6-10
6.4.5	Data Validation	6-11
6.5	MEDICAL RECORDS CODING QC.....	6-12
6.6	STATISTICAL ANALYSIS QC.....	6-12
6.7	ADMINISTRATIVE QA	6-13

REFERENCES.....	6-14
7 STATISTICAL METHODS.....	7-1
7.1 INTRODUCTION	7-1
7.2 MODELS AND ASSUMPTIONS	7-1
7.2.1 Model 1: Group and Occupation as Estimates of Exposure	7-2
7.2.2 Models 2 through 4: Serum Dioxin as an Estimate of Exposure.....	7-3
7.2.2.1 Prior Knowledge Regarding Dioxin	7-3
7.2.2.2 Fundamental Limitations of the Serum Dioxin Data.....	7-4
7.2.2.3 Model 2: Health versus Initial Dioxin in Ranch Hands.....	7-4
7.2.2.4 Model 3: Health versus Dioxin in Ranch Hands and Comparisons	7-6
7.2.2.5 Model 4: Health versus 1987 Dioxin in Ranch Hands	7-7
7.3 FACTORS DETERMINING THE STATISTICAL ANALYSIS METHOD.....	7-9
7.4 ANALYSIS METHODOLOGIES	7-11
7.4.1 Methods for Analyzing Continuous and Discrete Variables	7-11
7.4.2 Modeling Strategy.....	7-16
7.4.3 Longitudinal Analysis	7-16
7.5 INTERPRETIVE CONSIDERATIONS.....	7-17
7.5.1 Adjustments for Covariates	7-17
7.5.2 Multiple Testing.....	7-18
7.5.3 Trends	7-18
7.5.4 Interpretation of the Coefficient of Determination	7-18
7.5.5 Clinical Interpretation of Discrete versus Continuous Data	7-18
7.5.6 Power	7-19
7.6 EXPLANATION OF TABLES	7-21
7.6.1 Exposure Analysis	7-21
7.6.1.1 Continuous Variables	7-21
7.6.1.2 Discrete Variables.....	7-24
7.6.1.2.1 Discrete Variable with Two Categories	7-24
7.6.1.2.2 Discrete Variable with More Than Two Categories	7-26
7.6.2 Longitudinal Analysis.....	7-28
7.6.2.1 Continuous Variables	7-28
7.6.2.2 Discrete Variables with Two Categories	7-30
7.6.2.2.1 Discrete Variable with More Than Two Categories	7-32
REFERENCES.....	7-33
8 COVARIATE ASSOCIATIONS WITH ESTIMATES OF DIOXIN EXPOSURE	8-1
8.1 INTRODUCTION	8-1
8.2 MATCHING DEMOGRAPHIC VARIABLES (AGE, RACE, AND MILITARY OCCUPATION)	8-2
8.3 ALCOHOL USE.....	8-6
8.4 CIGARETTE SMOKING	8-6
8.5 EXPOSURE TO CARCINOGENS	8-16
8.6 HEALTH VARIABLES.....	8-22

8.7	SUN EXPOSURE VARIABLES	8-33
8.8	OTHER MISCELLANEOUS COVARIATES	8-41
8.9	SUMMARY	8-48
8.10	CONCLUSION.....	8-49
9	GENERAL HEALTH ASSESSMENT	9-1
9.1	INTRODUCTION	9-1
9.1.1	Background	9-1
9.1.2	Summary of Previous Analyses of the Air Force Health Study	9-3
9.1.2.1	1982 Baseline Study Summary Results	9-3
9.1.2.2	1985 Follow-up Study Summary Results	9-3
9.1.2.3	1987 Follow-up Study Summary Results	9-4
9.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	9-4
9.1.2.5	1992 Follow-up Study Summary Results	9-5
9.1.3	Parameters for the 1997 General Health Assessment	9-5
9.1.3.1	Dependent Variables.....	9-5
9.1.3.1.1	Questionnaire Data	9-5
9.1.3.1.2	Physical Examination Data.....	9-5
9.1.3.1.3	Laboratory Examination Data.....	9-6
9.1.3.2	Covariates	9-6
9.1.4	Statistical Methods.....	9-7
9.1.4.1	Longitudinal Analysis.....	9-9
9.2	RESULTS	9-10
9.2.1	Dependent Variable-Covariate Associations	9-10
9.2.2	Exposure Analysis	9-11
9.2.2.1	Questionnaire Variable	9-12
9.2.2.1.1	Self-perception of Health.....	9-12
9.2.2.2	Physical Examination Variables	9-15
9.2.2.2.1	Appearance of Illness or Distress as Assessed by Physician.....	9-15
9.2.2.2.2	Relative Age Appearance as Assessed by Physician.....	9-17
9.2.2.2.3	Body Fat (Continuous)	9-20
9.2.2.2.4	Body Fat (Discrete)	9-24
9.2.2.3	Laboratory Variable.....	9-26
9.2.2.3.1	Erythrocyte Sedimentation Rate (Continuous)	9-26
9.2.2.3.2	Erythrocyte Sedimentation Rate (Discrete)	9-30
9.2.3	Longitudinal Analysis	9-32
9.2.3.1	Questionnaire Variable	9-33
9.2.3.1.1	Self-perception of Health.....	9-33
9.2.3.2	Physical Examination Variables	9-36
9.2.3.2.1	Appearance of Illness or Distress	9-36
9.2.3.2.2	Relative Age Appearance	9-39
9.2.3.2.3	Body Fat (Continuous)	9-42
9.2.3.2.4	Body Fat (Discrete)	9-45
9.2.3.3	Laboratory Variable.....	9-48
9.2.3.3.1	Erythrocyte Sedimentation Rate (Continuous)	9-48
9.2.3.3.2	Erythrocyte Sedimentation Rate (Discrete)	9-51
9.3	DISCUSSION	9-55

9.4 SUMMARY	9-57
9.4.1 Model 1: Group Analysis.....	9-57
9.4.2 Model 2: Initial Dioxin Analysis	9-59
9.4.3 Model 3: Categorized Dioxin Analysis.....	9-60
9.4.4 Model 4: 1987 Dioxin Level Analysis.....	9-62
9.5 CONCLUSION.....	9-63
REFERENCES.....	9-65
10 NEOPLASIA ASSESSMENT.....	10-1
10.1 INTRODUCTION	10-1
10.1.1 Background.....	10-1
10.1.2 Summary of Previous Analyses of the Air Force Health Study	10-3
10.1.2.1 1982 Baseline Study Summary Results	10-3
10.1.2.2 1985 Follow-up Study Summary Results	10-3
10.1.2.3 1987 Follow-up Study Summary Results	10-4
10.1.2.4 Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	10-4
10.1.2.5 1992 Follow-up Study Summary Results	10-5
10.1.3 Parameters for the 1997 Neoplasia Assessment	10-5
10.1.3.1 Dependent Variables.....	10-5
10.1.3.1.1 Medical Records Data	10-5
10.1.3.1.2 Laboratory Examination Data.....	10-7
10.1.3.2 Covariates	10-7
10.1.4 Statistical Methods	10-8
10.1.4.1 Longitudinal Analysis.....	10-13
10.2 RESULTS	10-13
10.2.1 Dependent Variable-Covariate Associations.....	10-13
10.2.2 Exposure Analysis	10-18
10.2.2.1 Medical Records Review	10-19
10.2.2.1.1 Skin Neoplasms (All Sites Combined)	10-19
10.2.2.1.2 Malignant Skin Neoplasms	10-21
10.2.2.1.3 Benign Skin Neoplasms.....	10-24
10.2.2.1.4 Skin Neoplasms of Uncertain Behavior or Unspecified Nature	10-27
10.2.2.1.5 Basal Cell Carcinoma (All Sites Combined)	10-30
10.2.2.1.6 Basal Cell Carcinoma (Ear, Face, Head, and Neck).....	10-32
10.2.2.1.7 Basal Cell Carcinoma (Trunk).....	10-35
10.2.2.1.8 Basal Cell Carcinoma (Upper Extremities).....	10-37
10.2.2.1.9 Basal Cell Carcinoma (Lower Extremities).....	10-40
10.2.2.1.10 Squamous Cell Carcinoma	10-42
10.2.2.1.11 Nonmelanoma.....	10-45
10.2.2.1.12 Melanoma	10-47
10.2.2.1.13 Systemic Neoplasms (All Sites Combined).....	10-50
10.2.2.1.14 Malignant Systemic Neoplasms	10-52
10.2.2.1.15 Benign Systemic Neoplasms	10-55
10.2.2.1.16 Systemic Neoplasms of Uncertain Behavior or Unspecified Nature	10-57
10.2.2.1.17 Malignant Systemic Neoplasms (Eye, Ear, Face, Head, and Neck)	10-60
10.2.2.1.18 Malignant Systemic Neoplasms (Oral Cavity, Pharynx, and Larynx)	10-62
10.2.2.1.19 Malignant Systemic Neoplasms (Esophagus)	10-65

10.2.2.1.20	Malignant Systemic Neoplasms (Brain).....	10-65
10.2.2.1.21	Malignant Systemic Neoplasms (Thymus, Heart, and Mediastinum).....	10-65
10.2.2.1.22	Malignant Systemic Neoplasms (Thyroid Gland).....	10-68
10.2.2.1.23	Malignant Systemic Neoplasms (Bronchus and Lung).....	10-71
10.2.2.1.24	Malignant Systemic Neoplasms (Liver).....	10-75
10.2.2.1.25	Malignant Systemic Neoplasms (Colon and Rectum)	10-78
10.2.2.1.26	Malignant Systemic Neoplasms (Kidney and Bladder)	10-81
10.2.2.1.27	Malignant Systemic Neoplasms (Prostate)	10-84
10.2.2.1.28	Malignant Systemic Neoplasms (Testicles)	10-86
10.2.2.1.29	Malignant Systemic Neoplasms (Extrahepatic Bile Duct).....	10-89
10.2.2.1.30	Malignant Systemic Neoplasms (Ill-Defined Sites)	10-89
10.2.2.1.31	Malignant Systemic Neoplasms (Connective and Other Soft Tissues).....	10-89
10.2.2.1.32	Carcinoma In Situ (Penis)	10-93
10.2.2.1.33	Hodgkin's Disease.....	10-93
10.2.2.1.34	Non-Hodgkin's Lymphoma.....	10-96
10.2.2.1.35	Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	10-98
10.2.2.1.36	All Malignant Skin and Systemic Neoplasms	10-101
10.2.2.1.37	All Skin and Systemic Neoplasms	10-104
10.2.2.2	Laboratory Examination Variables	10-106
10.2.2.2.1	Prostate-Specific Antigen (PSA) (Continuous).....	10-106
10.2.2.2.2	PSA (Discrete).....	10-110
10.2.3	Longitudinal Analysis	10-113
10.2.3.1	Medical Records Review.....	10-113
10.2.3.1.1	Malignant Skin Neoplasms	10-113
10.2.3.1.2	Malignant Systemic Neoplasms	10-116
10.2.3.1.3	Benign Systemic Neoplasms	10-119
10.3	DISCUSSION	10-122
10.4	SUMMARY	10-124
10.4.1	Model 1: Group Analysis	10-124
10.4.2	Model 2: Initial Dioxin Analysis	10-128
10.4.3	Model 3: Categorized Dioxin Analysis	10-129
10.4.4	Model 4: 1987 Dioxin Analysis	10-133
10.5	CONCLUSION	10-134
REFERENCES	10-135
11	NEUROLOGICAL ASSESSMENT	11-1
11.1	INTRODUCTION	11-1
11.1.1	Background	11-1
11.1.2	Summary of Previous Analyses of the Air Force Health Study	11-3
11.1.2.1	1982 Baseline Study Summary Results.....	11-3
11.1.2.2	1985 Follow-up Study Summary Results	11-4
11.1.2.3	1987 Follow-up Study Summary Results	11-5
11.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	11-5
11.1.2.5	1992 Follow-up Study Summary Results	11-5
11.1.3	Parameters for the 1997 Neurological Assessment	11-5
11.1.3.1	Dependent Variables	11-5
11.1.3.1.1	Medical Records Variables	11-6

11.1.3.1.2	Physical Examination Data.....	11-6
11.1.3.2	Covariates	11-9
11.1.4	Statistical Methods	11-10
11.1.4.1	Longitudinal Analysis.....	11-14
11.2	RESULTS	11-14
11.2.1	Dependent Variable-Covariate Associations.....	11-14
11.2.2	Exposure Analysis	11-17
11.2.2.1	Medical Records Variables.....	11-18
11.2.2.1.1	Inflammatory Diseases	11-18
11.2.2.1.2	Hereditary and Degenerative Diseases	11-21
11.2.2.1.3	Peripheral Disorders	11-23
11.2.2.1.4	Other Neurological Disorders.....	11-26
11.2.2.2	Physical Examination Variables – Cranial Nerve Function	11-29
11.2.2.2.1	Smell	11-29
11.2.2.2.2	Visual Fields	11-31
11.2.2.2.3	Light Reaction	11-34
11.2.2.2.4	Ocular Movement	11-37
11.2.2.2.5	Facial Sensation.....	11-39
11.2.2.2.6	Corneal Reflex	11-42
11.2.2.2.7	Jaw Clench.....	11-43
11.2.2.2.8	Smile	11-45
11.2.2.2.9	Palpebral Fissure.....	11-48
11.2.2.2.10	Balance	11-51
11.2.2.2.11	Gag Reflex	11-53
11.2.2.2.12	Speech.....	11-54
11.2.2.2.13	Tongue Position Relative to Midline	11-56
11.2.2.2.14	Palate and Uvula Movement.....	11-59
11.2.2.2.15	Cranial Nerve Index	11-61
11.2.2.3	Physical Examination Variables – Musculoskeletal and Vertebral Column Function	11-64
11.2.2.3.1	Neck Range of Motion.....	11-64
11.2.2.4	Physical Examination Variables – Peripheral Nerve Status	11-67
11.2.2.4.1	Pinprick.....	11-67
11.2.2.4.2	Light Touch	11-69
11.2.2.4.3	Muscle Status.....	11-71
11.2.2.4.4	Patellar Reflex	11-74
11.2.2.4.5	Achilles Reflex	11-77
11.2.2.4.6	Biceps Reflex.....	11-79
11.2.2.4.7	Babinski Reflex	11-81
11.2.2.4.8	Polyneuropathy Severity Index.....	11-84
11.2.2.4.9	Polyneuropathy Prevalence Index	11-91
11.2.2.4.10	Multiple Polyneuropathy Index	11-93
11.2.2.4.11	Confirmed Polyneuropathy Indicator	11-96
11.2.2.5	Physical Examination Variables – CNS Coordination Processes	11-99
11.2.2.5.1	Tremor	11-99
11.2.2.5.2	Coordination	11-102
11.2.2.5.3	Romberg Sign	11-104
11.2.2.5.4	Gait	11-106

11.2.2.5.5	CNS Index.....	11-109
11.2.3	Longitudinal Analysis.....	11-111
11.2.3.1	Physical Examination Variables	11-112
11.2.3.1.1	Cranial Nerve Index.....	11-112
11.2.3.1.2	CNS Index.....	11-115
11.3	DISCUSSION.....	11-117
11.4	SUMMARY	11-119
11.4.1	Model 1: Group Analysis	11-119
11.4.2	Model 2: Initial Dioxin Analysis	11-121
11.4.3	Model 3: Categorized Dioxin Analysis	11-123
11.4.4	Model 4: 1987 Dioxin Analysis.....	11-126
11.5	CONCLUSION.....	11-127
REFERENCES	11-128
12	PSYCHOLOGICAL ASSESSMENT	12-1
12.1	INTRODUCTION	12-1
12.1.1	Background	12-1
12.1.2	Summary of Previous Analyses of the Air Force Health Study	12-2
12.1.2.1	1982 Baseline Study Summary Results	12-2
12.1.2.2	1985 Follow-up Study Summary Results	12-3
12.1.2.3	1987 Follow-up Study Summary Results	12-4
12.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	12-5
12.1.2.5	1992 Follow-up Study Summary Results	12-5
12.1.3	Parameters for the 1997 Psychological Assessment.....	12-5
12.1.3.1	Dependent Variables.....	12-5
12.1.3.1.1	Medical Records Data	12-5
12.1.3.1.2	Physical Examination Data.....	12-6
12.1.3.2	Covariates	12-6
12.1.4	Statistical Methods	12-7
12.2	RESULTS	12-10
12.2.1	Dependent Variable-Covariate Associations.....	12-10
12.2.2	Exposure Analysis	12-14
12.2.2.1	Medical Records Variables.....	12-15
12.2.2.1.1	Psychoses	12-15
12.2.2.1.2	Alcohol Dependence.....	12-17
12.2.2.1.3	Drug Dependence	12-19
12.2.2.1.4	Anxiety	12-22
12.2.2.1.5	Other Neuroses	12-25
12.2.2.2	Psychological Examination Variables	12-27
12.2.2.2.1	SCL-90-R Anxiety	12-28
12.2.2.2.2	SCL-90-R Depression.....	12-31
12.2.2.2.3	SCL-90-R Hostility	12-34
12.2.2.2.4	SCL-90-R Interpersonal Sensitivity.....	12-36
12.2.2.2.5	SCL-90-R Obsessive-Compulsive Behavior	12-39
12.2.2.2.6	SCL-90-R Paranoid Ideation	12-42
12.2.2.2.7	SCL-90-R Phobic Anxiety	12-45
12.2.2.2.8	SCL-90-R Psychoticism.....	12-48

12.2.2.2.9	SCL-90-R Somatization.....	12-51
12.2.2.2.10	SCL-90-R Global Severity Index (GSI).....	12-54
12.2.2.2.11	SCL-90-R Positive Symptom Total (PST)	12-57
12.2.2.2.12	SCL-90-R Positive Symptom Distress Index (PSDI)	12-59
12.3	DISCUSSION	12-62
12.4	SUMMARY	12-63
12.4.1	Model 1: Group Analysis	12-63
12.4.2	Model 2: Initial Dioxin Analysis	12-65
12.4.3	Model 3: Categorized Dioxin Analysis	12-65
12.4.4	Model 4: 1987 Dioxin Level Analysis	12-67
12.5	CONCLUSION	12-68
REFERENCES.....		12-69
13	GASTROINTESTINAL ASSESSMENT.....	13-1
13.1	INTRODUCTION	13-1
13.1.1	Background	13-1
13.1.2	Summary of Previous Analyses of the Air Force Health Study	13-2
13.1.2.1	1982 Baseline Study Summary Results	13-2
13.1.2.2	1985 Follow-up Study Summary Results	13-2
13.1.2.3	1987 Follow-up Study Summary Results	13-3
13.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	13-3
13.1.2.5	1992 Follow-up Study Summary Results	13-3
13.1.3	Parameters for the 1997 Gastrointestinal Assessment.....	13-4
13.1.3.1	Dependent Variables.....	13-4
13.1.3.1.1	Medical Records Data	13-4
13.1.3.1.2	Physical Examination Data.....	13-4
13.1.3.1.3	Laboratory Examination Data.....	13-5
13.1.3.2	Covariates	13-5
13.1.4	Statistical Methods	13-6
13.1.4.1	Longitudinal Analysis.....	13-11
13.2	RESULTS	13-11
13.2.1	Dependent Variable-Covariate Associations.....	13-11
13.2.1.1	Medical Records Variables.....	13-11
13.2.1.2	Laboratory Examination Variables.....	13-12
13.2.2	Exposure Analysis	13-17
13.2.2.1	Medical Records Variables.....	13-18
13.2.2.1.1	Uncharacterized Hepatitis	13-18
13.2.2.1.2	Jaundice (Unspecified)	13-21
13.2.2.1.3	Acute Necrosis of the Liver	13-24
13.2.2.1.4	Chronic Liver Disease and Cirrhosis (Alcohol-related).....	13-24
13.2.2.1.5	Chronic Liver Disease and Cirrhosis (Non-alcohol-related)	13-26
13.2.2.1.6	Liver Abscess and Sequelae of Chronic Liver Disease	13-29
13.2.2.1.7	Enlarged Liver (Hepatomegaly)	13-31
13.2.2.1.8	Other Liver Disorders	13-34
13.2.2.2	Physical Examination Variables	13-36
13.2.2.2.1	Current Hepatomegaly	13-36
13.2.2.3	Laboratory Examination Variables.....	13-39

13.2.2.3.1	AST (Continuous).....	13-39
13.2.2.3.2	AST (Discrete).....	13-42
13.2.2.3.3	ALT (Continuous)	13-45
13.2.2.3.4	ALT (Discrete)	13-48
13.2.2.3.5	GGT (Continuous)	13-50
13.2.2.3.6	GGT (Discrete)	13-54
13.2.2.3.7	Alkaline Phosphatase (Continuous).....	13-56
13.2.2.3.8	Alkaline Phosphatase (Discrete).....	13-59
13.2.2.3.9	Total Bilirubin (Continuous)	13-62
13.2.2.3.10	Total Bilirubin (Discrete)	13-64
13.2.2.3.11	Direct Bilirubin.....	13-67
13.2.2.3.12	Lactic Dehydrogenase (Continuous)	13-69
13.2.2.3.13	Lactic Dehydrogenase (Discrete)	13-72
13.2.2.3.14	Cholesterol (Continuous).....	13-74
13.2.2.3.15	Cholesterol (Discrete).....	13-77
13.2.2.3.16	HDL Cholesterol (Continuous)	13-80
13.2.2.3.17	HDL Cholesterol (Discrete).....	13-82
13.2.2.3.18	Cholesterol-HDL Ratio (Continuous)	13-85
13.2.2.3.19	Cholesterol-HDL Ratio (Discrete).....	13-88
13.2.2.3.20	Triglycerides (Continuous).....	13-91
13.2.2.3.21	Triglycerides (Discrete).....	13-94
13.2.2.3.22	Creatine Phosphokinase (Continuous).....	13-97
13.2.2.3.23	Creatine Phosphokinase (Discrete).....	13-100
13.2.2.3.24	Serum Amylase (Continuous).....	13-102
13.2.2.3.25	Serum Amylase (Discrete).....	13-105
13.2.2.3.26	Antibodies for Hepatitis A.....	13-108
13.2.2.3.27	Evidence of Prior Hepatitis B	13-110
13.2.2.3.28	Current Hepatitis B	13-112
13.2.2.3.29	Antibodies for Hepatitis C	13-115
13.2.2.3.30	Antibodies for Hepatitis D	13-117
13.2.2.3.31	Stool Hemoccult	13-117
13.2.2.3.32	Prealbumin (Continuous).....	13-120
13.2.2.3.33	Prealbumin (Discrete).....	13-122
13.2.2.3.34	Albumin (Continuous).....	13-125
13.2.2.3.35	Albumin (Discrete)	13-127
13.2.2.3.36	α -1-Acid Glycoprotein (Continuous)	13-130
13.2.2.3.37	α -1-Acid Glycoprotein (Discrete)	13-133
13.2.2.3.38	α -1-Antitrypsin (Continuous)	13-135
13.2.2.3.39	α -1-Antitrypsin (Discrete)	13-139
13.2.2.3.40	α -2-Macroglobulin (Continuous)	13-144
13.2.2.3.41	α -2-Macroglobulin (Discrete)	13-147
13.2.2.3.42	Apolipoprotein B (mg/dl) (Continuous)	13-149
13.2.2.3.43	Apolipoprotein B (Discrete)	13-152
13.2.2.3.44	C3 Complement (mg/dl) (Continuous)	13-155
13.2.2.3.45	C3 Complement (Discrete)	13-158
13.2.2.3.46	C4 Complement (Continuous)	13-161
13.2.2.3.47	C4 Complement (Discrete)	13-164
13.2.2.3.48	Haptoglobin (Continuous)	13-166
13.2.2.3.49	Haptoglobin (Discrete)	13-169

13.2.2.3.50	Transferrin (Continuous)	13-172
13.2.2.3.51	Transferrin (Discrete)	13-175
13.2.3	Longitudinal Analysis.....	13-178
13.2.3.1	Laboratory Examination Variables	13-179
13.2.3.1.1	AST (Continuous).....	13-179
13.2.3.1.2	AST (Discrete).....	13-182
13.2.3.1.3	ALT (Continuous)	13-184
13.2.3.1.4	ALT (Discrete)	13-187
13.2.3.1.5	GGT (Continuous)	13-189
13.2.3.1.6	GGT (Discrete)	13-192
13.2.3.1.7	Cholesterol (Continuous).....	13-194
13.2.3.1.8	Cholesterol (Discrete).....	13-197
13.2.3.1.9	HDL Cholesterol (Continuous)	13-199
13.2.3.1.10	HDL Cholesterol (Discrete).....	13-202
13.2.3.1.11	Cholesterol-HDL Ratio (Continuous)	13-204
13.2.3.1.12	Cholesterol-HDL Ratio (Discrete).....	13-207
13.2.3.1.13	Triglycerides (Continuous).....	13-209
13.2.3.1.14	Triglycerides (Discrete).....	13-212
13.3	DISCUSSION	13-214
13.4	SUMMARY	13-217
13.4.1	Model 1: Group Analysis	13-217
13.4.2	Model 2: Initial Dioxin Analysis	13-221
13.4.3	Model 3: Categorized Dioxin Analysis	13-223
13.4.4	Model 4: 1987 Dioxin Level Analysis	13-227
13.5	CONCLUSION.....	13-229
REFERENCES	13-231
14 CARDIOVASCULAR ASSESSMENT	14-1
14.1	INTRODUCTION	14-1
14.1.1	Background	14-1
14.1.2	Summary of Previous Analyses of the Air Force Health Study	14-2
14.1.2.1	1982 Baseline Study Summary Results	14-2
14.1.2.2	1985 Follow-up Study Summary Results	14-3
14.1.2.3	1987 Follow-up Study Summary Results	14-3
14.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	14-3
14.1.2.5	1992 Follow-up Study Summary Results	14-4
14.1.3	Parameters for the 1997 Cardiovascular Assessment	14-4
14.1.3.1	Dependent Variables.....	14-4
14.1.3.1.1	Medical Records Data	14-4
14.1.3.1.2	Physical Examination Data and Self-reported Questionnaire Data.....	14-5
14.1.3.2	Covariates	14-6
14.1.4	Statistical Methods	14-8
14.1.4.1	Longitudinal Analysis.....	14-12
14.2	RESULTS	14-12
14.2.1	Dependent Variable-Covariate Associations	14-12
14.2.2	Exposure Analysis	14-17
14.2.2.1	Medical Records Variables.....	14-18

14.2.2.1.1	Essential Hypertension	14-18
14.2.2.1.2	Heart Disease (Excluding Essential Hypertension).....	14-20
14.2.2.1.3	Myocardial Infarction	14-23
14.2.2.1.4	Stroke or Transient Ischemic Attack	14-25
14.2.2.2	Physical Examination Variables – Central Cardiac Function	14-28
14.2.2.2.1	Systolic Blood Pressure (Continuous).....	14-28
14.2.2.2.2	Systolic Blood Pressure (Discrete).....	14-31
14.2.2.2.3	Diastolic Blood Pressure (Continuous)	14-34
14.2.2.2.4	Diastolic Blood Pressure (Discrete)	14-38
14.2.2.2.5	Heart Sounds.....	14-40
14.2.2.2.6	Overall Electrocardiograph.....	14-42
14.2.2.2.7	Right Bundle Branch Block	14-45
14.2.2.2.8	Left Bundle Branch Block	14-47
14.2.2.2.9	Non-Specific ST- and T-Wave Changes	14-50
14.2.2.2.10	Bradycardia.....	14-52
14.2.2.2.11	Tachycardia	14-54
14.2.2.2.12	Arrhythmia.....	14-57
14.2.2.2.13	Evidence of Prior Myocardial Infarction.....	14-60
14.2.2.2.14	ECG: Other Diagnoses	14-63
14.2.2.3	Physical Examination Variables – Peripheral Vascular Function.....	14-66
14.2.2.3.1	Funduscopic Examination	14-66
14.2.2.3.2	Carotid Bruits	14-68
14.2.2.3.3	Radial Pulses.....	14-71
14.2.2.3.4	Femoral Pulses.....	14-74
14.2.2.3.5	Popliteal Pulses.....	14-76
14.2.2.3.6	Dorsalis Pedis Pulses	14-78
14.2.2.3.7	Posterior Tibial Pulses	14-81
14.2.2.3.8	Leg Pulses	14-83
14.2.2.3.9	Peripheral Pulses.....	14-85
14.2.2.3.10	ICVI Index	14-88
14.2.3	Longitudinal Analysis.....	14-90
14.2.3.1	Physical Examination Variables	14-91
14.2.3.1.1	Systolic Blood Pressure (Continuous).....	14-91
14.2.3.1.2	Systolic Blood Pressure (Discrete).....	14-94
14.2.3.1.3	Femoral Pulses.....	14-97
14.2.3.1.4	Popliteal Pulses	14-100
14.2.3.1.5	Dorsalis Pedis Pulses	14-103
14.2.3.1.6	Posterior Tibial Pulses	14-105
14.2.3.1.7	Leg Pulses	14-108
14.2.3.1.8	Peripheral Pulses.....	14-110
14.3	DISCUSSION.....	14-113
14.4	SUMMARY	14-115
14.4.1	Model 1: Group Analysis	14-115
14.4.2	Model 2: Initial Dioxin Analysis	14-118
14.4.3	Model 3: Categorized Dioxin Analysis	14-119
14.4.4	Model 4: 1987 Dioxin Level Analysis	14-121
14.5	CONCLUSION.....	14-122

REFERENCES.....	14-124
15 HEMATOLOGIC ASSESSMENT	15-1
15.1 INTRODUCTION	15-1
15.1.1 Background	15-1
15.1.2 Summary of Previous Analyses of the Air Force Health Study	15-2
15.1.2.1 1982 Baseline Study Summary Results	15-2
15.1.2.2 1985 Follow-up Study Summary Results	15-3
15.1.2.3 1987 Follow-up Study Summary Results	15-3
15.1.2.4 Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	15-4
15.1.2.5 1992 Follow-up Study Summary Results	15-4
15.1.3 Parameters for the 1997 Hematologic Assessment	15-5
15.1.3.1 Dependent Variables.....	15-5
15.1.3.1.1 Laboratory Examination Data.....	15-5
15.1.3.2 Covariates	15-5
15.1.4 Statistical Methods	15-5
15.1.4.1 Longitudinal Analysis.....	15-8
15.2 RESULTS	15-8
15.2.1 Dependent Variable-Covariate Associations.....	15-8
15.2.2 Exposure Analysis	15-12
15.2.2.1 Laboratory Examination Variables.....	15-13
15.2.2.1.1 RBC Count (Continuous)	15-13
15.2.2.1.2 RBC Count (Discrete)	15-15
15.2.2.1.3 WBC Count (Continuous)	15-20
15.2.2.1.4 WBC Count (Discrete)	15-23
15.2.2.1.5 Hemoglobin (Continuous)	15-28
15.2.2.1.6 Hemoglobin (Discrete)	15-31
15.2.2.1.7 Hematocrit (Continuous)	15-37
15.2.2.1.8 Hematocrit (Discrete)	15-39
15.2.2.1.9 Platelet Count (Continuous)	15-45
15.2.2.1.10 Platelet Count (Discrete)	15-48
15.2.2.1.11 Prothrombin Time (Continuous)	15-54
15.2.2.1.12 Prothrombin Time (Discrete).....	15-57
15.2.2.1.13 RBC Morphology	15-59
15.2.2.1.14 Absolute Neutrophils (Segs).....	15-61
15.2.2.1.15 Absolute Neutrophils (Bands) (Nonzero Measurements)	15-65
15.2.2.1.16 Absolute Neutrophils (Bands) (Zero versus Nonzero)	15-68
15.2.2.1.17 Absolute Lymphocytes	15-71
15.2.2.1.18 Absolute Monocytes	15-74
15.2.2.1.19 Absolute Eosinophils (Nonzero Measurements)	15-78
15.2.2.1.20 Absolute Eosinophils (Zero versus Nonzero).....	15-81
15.2.2.1.21 Absolute Basophils (Nonzero Measurements)	15-84
15.2.2.1.22 Absolute Basophils (Zero versus Nonzero).....	15-86
15.2.3 Longitudinal Analysis.....	15-89
15.2.3.1 Laboratory Variable.....	15-90
15.2.3.1.1 Platelet Count (Continuous)	15-90
15.2.3.1.2 Platelet Count (Discrete)	15-93
15.3 DISCUSSION	15-99

15.4 SUMMARY	15-101
15.4.1 Model 1: Group Analysis	15-101
15.4.2 Model 2: Initial Dioxin Analysis	15-104
15.4.3 Model 3: Categorized Dioxin Analysis	15-105
15.4.4 Model 4: 1987 Dioxin.....	15-109
15.5 CONCLUSION.....	15-110
REFERENCES.....	15-111
16 ENDOCRINE ASSESSMENT	16-1
16.1 INTRODUCTION	16-1
16.1.1 Background.....	16-1
16.1.2 Summary of Previous Analyses of the Air Force Health Study	16-3
16.1.2.1 1982 Baseline Study Summary Results	16-3
16.1.2.2 1985 Follow-up Study Summary Results	16-3
16.1.2.3 1987 Follow-up Study Summary Results	16-4
16.1.2.4 Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	16-4
16.1.2.5 1992 Follow-up Study Summary Results	16-4
16.1.3 Parameters for the 1997 Endocrine Assessment.....	16-5
16.1.3.1 Dependent Variables.....	16-5
16.1.3.2 Medical Records Data.....	16-5
16.1.3.2.1 Physical Examination Data.....	16-6
16.1.3.2.2 Laboratory Examination Data.....	16-6
16.1.3.3 Covariates	16-7
16.1.4 Statistical Methods	16-7
16.2 RESULTS	16-11
16.2.1 Dependent Variable-Covariate Associations.....	16-11
16.2.2 Exposure Analysis	16-15
16.2.2.1 Medical Records Variables.....	16-16
16.2.2.1.1 Past Thyroid Disease	16-16
16.2.2.1.2 Composite Diabetes Indicator.....	16-18
16.2.2.1.3 Diabetic Severity	16-21
16.2.2.1.4 Time to Diabetes Onset	16-29
16.2.2.2 Physical Examination Variables	16-32
16.2.2.2.1 Thyroid Gland.....	16-32
16.2.2.2.2 Testicular Examination.....	16-34
16.2.2.3 Laboratory Examination Variables	16-37
16.2.2.3.1 TSH (Continuous).....	16-37
16.2.2.3.2 TSH (Discrete).....	16-40
16.2.2.3.3 Thyroxine (Continuous)	16-46
16.2.2.3.4 Thyroxine (Discrete).....	16-49
16.2.2.3.5 Anti-Thyroid Antibodies	16-51
16.2.2.3.6 Fasting Glucose (Continuous)	16-53
16.2.2.3.7 Fasting Glucose (Discrete)	16-57
16.2.2.3.8 2-Hour Postprandial Glucose (Continuous)	16-59
16.2.2.3.9 2-Hour Postprandial Glucose (Discrete).....	16-63
16.2.2.3.10 Fasting Urinary Glucose	16-65
16.2.2.3.11 2-Hour Postprandial Urinary Glucose	16-67

16.2.2.3.12	Serum Insulin (Continuous).....	16-70
16.2.2.3.13	Serum Insulin (Discrete).....	16-74
16.2.2.3.14	α -1-C Hemoglobin (Continuous).....	16-80
16.2.2.3.15	α -1-C Hemoglobin (Discrete).....	16-83
16.2.2.3.16	Total Testosterone (Continuous)	16-86
16.2.2.3.17	Total Testosterone (Discrete)	16-89
16.2.2.3.18	Free Testosterone (Continuous)	16-91
16.2.2.3.19	Free Testosterone (Discrete).....	16-94
16.2.2.3.20	Estradiol (Continuous).....	16-97
16.2.2.3.21	Estradiol (Discrete).....	16-100
16.2.2.3.22	LH (Continuous).....	16-102
16.2.2.3.23	LH (Discrete).....	16-106
16.2.2.3.24	FSH (Continuous).....	16-108
16.2.2.3.25	FSH (Discrete).....	16-111
16.2.3	Longitudinal Analysis.....	16-114
16.2.3.1	Medical Records Variables.....	16-115
16.2.3.1.1	Composite Diabetes Indicator.....	16-115
16.2.3.2	Laboratory Examination Variables.....	16-118
16.2.3.2.1	TSH (Continuous).....	16-118
16.2.3.2.2	TSH (Discrete).....	16-120
16.2.3.2.3	Fasting Glucose (Continuous)	16-122
16.2.3.2.4	Fasting Glucose (Discrete)	16-124
16.2.3.2.5	2-Hour Postprandial Glucose (Continuous)	16-127
16.2.3.2.6	2-Hour Postprandial Glucose (Discrete).....	16-130
16.2.3.2.7	Total Testosterone (Continuous)	16-133
16.2.3.2.8	Total Testosterone (Discrete)	16-136
16.3	DISCUSSION.....	16-139
16.4	SUMMARY	16-141
16.4.1	Model 1: Group Analysis	16-141
16.4.2	Model 2: Initial Dioxin Analysis	16-144
16.4.3	Model 3: Categorized Dioxin Analysis	16-145
16.4.4	Model 4: 1987 Dioxin Level Analysis	16-148
16.5	CONCLUSION.....	16-150
REFERENCES.....		16-151
17	IMMUNOLOGIC ASSESSMENT.....	17-1
17.1	INTRODUCTION	17-1
17.1.1	Background	17-1
17.1.2	Summary of Previous Analyses of the Air Force Health Study	17-2
17.1.2.1	1982 Baseline Study Summary Results	17-2
17.1.2.2	1985 Follow-up Summary Results	17-3
17.1.2.3	1987 Follow-up Study Summary Results	17-4
17.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	17-4
17.1.2.5	1992 Follow-up Study Summary Results	17-5
17.1.3	Parameters for the 1997 Immunologic Assessment.....	17-5
17.1.3.1	Dependent Variables.....	17-5
17.1.3.1.1	Laboratory Examination Data.....	17-7

17.1.3.1.1.1	Cell Surface Marker (Phenotypic) Studies	17-8
17.1.3.1.1.2	Absolute Lymphocytes	17-8
17.1.3.1.1.3	Immunoglobulins	17-8
17.1.3.1.1.4	Lupus Panel	17-8
17.1.3.2	Covariates	17-9
17.1.4	Statistical Methods	17-10
17.2 RESULTS	17-13
17.2.1	Dependent Variable-Covariate Associations.....	17-13
17.2.2	Exposure Analysis	17-16
17.2.2.1	Laboratory Variables	17-17
17.2.2.1.1	CD3+ Cells (T Cells)	17-17
17.2.2.1.2	CD4+ Cells (Helper T Cells)	17-20
17.2.2.1.3	CD8+ Cells (Suppressor T Cells)	17-23
17.2.2.1.4	CD16+56+ Cells (Natural Killer Cells).....	17-26
17.2.2.1.5	CD20+ Cells (B Cells).....	17-29
17.2.2.1.6	CD3+CD4+ Cells (Helper T Cells)	17-32
17.2.2.1.7	Absolute Lymphocytes	17-35
17.2.2.1.8	IgA	17-38
17.2.2.1.9	IgG	17-41
17.2.2.1.10	IgM.....	17-44
17.2.2.1.11	Lupus Panel: ANA Test	17-47
17.2.2.1.12	Lupus Panel: Thyroid Microsomal Antibody	17-49
17.2.2.1.13	Lupus Panel: MSK Smooth Muscle Antibody	17-51
17.2.2.1.14	Lupus Panel: MSK Mitochondrial Antibody	17-54
17.2.2.1.15	Lupus Panel: MSK Parietal Antibody	17-57
17.2.2.1.16	Lupus Panel: Rheumatoid Factor	17-60
17.3 DISCUSSION	17-63
17.4 SUMMARY	17-66
17.4.1	Model 1: Group Analysis	17-66
17.4.2	Model 2: Initial Dioxin Analysis	17-68
17.4.3	Model 3: Categorized Dioxin Analysis	17-69
17.4.4	Model 4: 1987 Dioxin Level Analysis	17-71
17.5 CONCLUSION	17-72
REFERENCES	17-74
18 PULMONARY ASSESSMENT	18-1
18.1 INTRODUCTION	18-1
18.1.1	Background	18-1
18.1.2	Summary of Previous Analyses of the Air Force Health Study	18-2
18.1.2.1	1982 Baseline Study Summary Results	18-2
18.1.2.2	1985 Follow-up Study Summary Results	18-3
18.1.2.3	1987 Follow-up Study Summary Results	18-3
18.1.2.4	Serum Dioxin Analysis of 1987 Follow-up Study Summary Results	18-3
18.1.2.5	1992 Follow-up Study Summary Results	18-4
18.1.3	Parameters for the 1997 Pulmonary Assessment	18-4
18.1.3.1	Dependent Variables.....	18-4
18.1.3.1.1	Medical Records Data	18-4

18.1.3.1.2	Physical Examination Data.....	18-5
18.1.3.1.3	Laboratory Examination Data.....	18-5
18.1.3.2	Covariates	18-6
18.1.4	Statistical Methods	18-6
18.1.4.1	Longitudinal Analysis.....	18-9
18.2	RESULTS	18-9
18.2.1	Dependent Variable-Covariate Associations.....	18-9
18.2.2	Exposure Analysis	18-11
18.2.2.1	Medical Records Variables.....	18-12
18.2.2.1.1	Asthma.....	18-12
18.2.2.1.2	Bronchitis.....	18-14
18.2.2.1.3	Pneumonia	18-17
18.2.2.2	Physical Examination Variable.....	18-19
18.2.2.2.1	Thorax and Lung Abnormalities.....	18-19
18.2.2.3	Laboratory Examination Variables	18-22
18.2.2.3.1	X-ray Interpretation	18-22
18.2.2.3.2	FVC (Percent of Predicted)	18-24
18.2.2.3.3	FEV ₁ (Percent of Predicted)	18-27
18.2.2.3.4	Ratio of Observed FEV ₁ to Observed FVC	18-29
18.2.2.3.5	Loss of Vital Capacity	18-32
18.2.2.3.6	Obstructive Abnormality	18-37
18.2.3	Longitudinal Analysis.....	18-41
18.2.3.1	Laboratory Examination Variable	18-42
18.2.3.1.1	Ratio of Observed FEV ₁ to Observed FVC	18-42
18.3	DISCUSSION	18-44
18.4	SUMMARY	18-46
18.4.1	Model 1: Group Analysis	18-46
18.4.2	Model 2: Initial Dioxin Analysis	18-48
18.4.3	Model 3: Categorized Dioxin Analysis	18-49
18.4.4	Model 4: 1987 Dioxin Level Analysis	18-51
18.5	CONCLUSION.....	18-52
REFERENCES	18-54
19 CONCLUSIONS	19-1
19.1	INTRODUCTION	19-1
19.2	STUDY PERFORMANCE ASPECTS	19-1
19.3	STATISTICAL MODELS	19-1
19.4	CLINICAL RESULTS	19-3
19.4.1	General Health Assessment	19-3
19.4.2	Malignant Neoplastic Diseases.....	19-4
19.4.3	Neurological Assessment.....	19-4
19.4.4	Psychological Assessment	19-4
19.4.5	Gastrointestinal Assessment	19-5
19.4.6	Cardiovascular Assessment	19-6
19.4.7	Hematologic Assessment	19-6

19.4.8	Endocrine Assessment	19-7
19.4.9	Immunologic Assessment	19-7
19.4.10	Pulmonary Assessment	19-8
19.5	INTERPRETIVE CONSIDERATIONS	19-8
19.6	SUMMARY	19-9
19.6.1	Diabetes	19-9
19.6.2	Cardiovascular Abnormalities	19-9
19.6.3	Peripheral Polyneuropathy	19-10
19.6.4	Serum Lipid Abnormalities	19-10
19.6.5	Liver Enzymes	19-10
19.6.6	Malignant Neoplastic Disease	19-10
19.7	CONCLUSION	19-11
20	FUTURE DIRECTIONS	20-1
Appendix A.	Policies and Procedures for Dioxin Blood Collection Processing.....	A-1
Appendix B.	Physical Examination Methodology	B-1
Appendix C.	Study Selection and Participation	C-1
Appendix D.	Coefficients Of Variation For Quality Control.....	D-1
Appendix E.	Statistical Methods	E-1
Appendix F.	Dependent Variable-Covariate Associations.....	F-1
Appendix G.	Summary of Analysis Results	G-1

List of Tables

Table 1-1.	Parameters of Exposure Assessment Models	1-7
Table 2-1.	Participants with a 1997 Blood Measurement of Dioxin	2-1
Table 2-2.	Participants Eligible for the 1997 Blood Measurement of Dioxin and Reasons for Participant Sample Exclusions.....	2-2
Table 2-3.	Result Comments for the 1997 Blood Measurements of Dioxin	2-3
Table 2-4.	Dioxin Results for 1997 Physical Examination Participants	2-3
Table 2-5.	Results from Blood Measurements of Dioxin.....	2-5
Table 2-6.	Results from Blood Measurements of Dioxin with Missing or Nonquantitative Results.....	2-5
Table 2-7.	Summary of Number of Assays Used for 1997 Follow-up Participant Dioxin Measures	2-6
Table 2-8.	Lipid-adjusted Dioxin Result Summary	2-9
Table 4-1.	Elements of the 1997 Follow-up Physical Examination	4-2
Table 4-2.	Laboratory Test Procedures Performed at Scripps Clinic	4-2
Table 5-1.	Compliance by Group and Examination Year	5-7
Table 5-2.	Participants Newly Compliant in 1997 and Their Previous Compliance Pattern	5-8
Table 5-3.	Reasons for Refusal by Group	5-10
Table 5-4.	Reasons for Refusal by Group, Age, Rank, and Race	5-11
Table 5-5.	Reasons for Refusal by Group and Year	5-13
Table 5-6.	Self-reported Health Status of Original Comparisons and Their Replacements.....	5-14
Table 5-7.	Matched Set Compliance of Noncompliant Original Comparisons	5-15
Table 5-8.	Reported Health Status of Refusals.....	5-15
Table 5-9.	Reported Health Status of Passive Refusals.....	5-16
Table 5-10.	Reported Health Status by Group, Age, Rank, Compliance, and Race	5-17
Table 5-11.	Reported Health Status by Group.....	5-17
Table 5-12.	Reported Health Status of Fully Compliant Participants	5-18
Table 5-13.	Reported Medication Use of Fully Compliant Participants	5-18
Table 5-14.	Reported Work Loss of Fully Compliant Participants	5-18
Table 7-1.	Model 1: Assessing Health versus Group Status in Ranch Hands and Comparisons: Assumptions, Advantages, and Disadvantages	7-3
Table 7-2.	Model 2: Assessing Health versus Initial Dioxin in Ranch Hands: Assumptions, Advantages, and Disadvantages	7-5
Table 7-3.	Model 3: Assessing Health versus Categorized Dioxin in Ranch Hands and Comparisons.....	7-7

Table 7-4.	Model 4: Assessing Health versus 1987 Dioxin in Ranch Hands: Assumptions, Advantages, and Disadvantages	7-8
Table 7-5.	Summary of Statistical Analysis Situations by Dependent Variable Form, Exposure Estimate, Analysis Cohort, and Analysis Type.....	7-9
Table 7-6.	Summary of Statistical Procedures	7-12
Table 7-7.	Approximate Power To Detect a Group Effect at a 5-Percent Level of Significance (Discrete Dependent Variable)	7-19
Table 7-8.	Approximate Power To Detect a Group Effect at a 5-Percent Level of Significance (Continuous Dependent Variable)	7-20
Table 7-9.	Location of Table Results from Different Exposure Analysis Models.....	7-21
Table 7-10.	Location of Table Results from Different Longitudinal Analysis Models	7-28
Table 8-1.	Associations Between Matching Demographic Variables (Age, Race, and Military Occupation) and Estimates of Herbicide or Dioxin Exposure.....	8-3
Table 8-2.	Associations Between Alcohol Use and Estimates of Herbicide or Dioxin Exposure	8-7
Table 8-3.	Associations Between Cigarette Smoking and Estimates of Herbicide or Dioxin Exposure.....	8-13
Table 8-4.	Associations Between Exposure to Carcinogens and Estimates of Herbicide or Dioxin Exposure	8-17
Table 8-5.	Associations Between Health Variables and Estimates of Herbicide or Dioxin Exposure.....	8-23
Table 8-6.	Associations Between Sun Exposure Variables and Estimates of Herbicide or Dioxin Exposure (Non-Blacks Only).....	8-34
Table 8-7.	Associations Between Other Miscellaneous Covariates and Estimates of Herbicide or Dioxin Exposure	8-42
Table 9-1.	Statistical Analysis for the General Health Assessment	9-7
Table 9-2.	Number of Participants with Missing Data for the General Health Assessment	9-9
Table 9-3.	Analysis of Self-perception of Health.....	9-13
Table 9-4.	Analysis of Appearance of Illness or Distress	9-15
Table 9-5.	Analysis of Relative Age Appearance.....	9-18
Table 9-6.	Analysis of Body Fat (Percent) (Continuous)	9-21
Table 9-7.	Analysis of Body Fat (Discrete).....	9-24
Table 9-8.	Analysis of Erythrocyte Sedimentation Rate (mm/hr) (Continuous)	9-27
Table 9-9.	Analysis of Erythrocyte Sedimentation Rate (Discrete)	9-30
Table 9-10.	Longitudinal Analysis of Self-perception of Health	9-34
Table 9-11.	Longitudinal Analysis of Appearance of Illness or Distress	9-37
Table 9-12.	Longitudinal Analysis of Relative Age Appearance	9-40
Table 9-13.	Longitudinal Analysis of Body Fat (Percent) (Continuous)	9-43

Table 9-14. Longitudinal Analysis of Body Fat (Discrete)	9-46
Table 9-15. Longitudinal Analysis of Erythrocyte Sedimentation Rate (mm/hr) (Continuous)	9-49
Table 9-16. Longitudinal Analysis of Erythrocyte Sedimentation Rate (Discrete)	9-52
Table 9-17. Summary of Group Analysis (Model 1) for General Health Variables (Ranch Hands vs. Comparisons).....	9-58
Table 9-18. Summary of Initial Dioxin Analysis (Model 2) for General Health Variables (Ranch Hands Only).....	9-59
Table 9-19. Summary of Categorized Dioxin Analysis (Model 3) for General Health Variables (Ranch Hands vs. Comparisons)	9-61
Table 9-20. Summary of 1987 Dioxin Analysis (Model 4) for General Health Variables (Ranch Hands Only).....	9-63
Table 10-1. Statistical Analysis for the Neoplasia Assessment.....	10-9
Table 10-2. Number of Participants Excluded or with Missing Data for the Neoplasia Assessment.....	10-13
Table 10-3. Analysis of Skin Neoplasms.....	10-19
Table 10-4. Analysis of Malignant Skin Neoplasms	10-22
Table 10-5. Analysis of Benign Skin Neoplasms	10-24
Table 10-6. Analysis of Skin Neoplasms of Uncertain Behavior or Unspecified Nature	10-27
Table 10-7. Analysis of Basal Cell Carcinoma (All Sites Combined)	10-30
Table 10-8. Analysis of Basal Cell Carcinoma (Ear, Face, Head, and Neck)	10-33
Table 10-9. Analysis of Basal Cell Carcinoma (Trunk)	10-35
Table 10-10. Analysis of Basal Cell Carcinoma (Upper Extremities)	10-38
Table 10-11. Analysis of Basal Cell Carcinoma (Lower Extremities)	10-40
Table 10-12. Analysis of Squamous Cell Carcinoma	10-43
Table 10-13. Analysis of Nonmelanoma	10-45
Table 10-14. Analysis of Melanoma.....	10-48
Table 10-15. Analysis of Systemic Neoplasms (All Sites Combined)	10-50
Table 10-16. Analysis of Malignant Systemic Neoplasms	10-53
Table 10-17. Analysis of Benign Systemic Neoplasms	10-55
Table 10-18. Analysis of Systemic Neoplasms of Uncertain Behavior or Unspecified Nature	10-58
Table 10-19. Analysis of Malignant Systemic Neoplasms (Eye, Ear, Face, Head, and Neck)	10-60
Table 10-20. Analysis of Malignant Systemic Neoplasms (Oral Cavity, Pharynx, and Larynx).....	10-63
Table 10-21. Analysis of Malignant Systemic Neoplasms (Thymus, Heart, and Mediastinum)	10-66
Table 10-22. Analysis of Malignant Systemic Neoplasms (Thyroid Gland)	10-68
Table 10-23. Analysis of Malignant Systemic Neoplasms (Bronchus and Lung).....	10-72

Table 10-24. Analysis of Malignant Systemic Neoplasms (Liver)	10-75
Table 10-25. Analysis of Malignant Systemic Neoplasms (Colon and Rectum)	10-78
Table 10-26. Analysis of Malignant Systemic Neoplasms (Kidney and Bladder)	10-81
Table 10-27. Analysis of Malignant Systemic Neoplasms (Prostate)	10-84
Table 10-28. Analysis of Malignant Systemic Neoplasms (Testicles).....	10-87
Table 10-29. Analysis of Malignant Systemic Neoplasms (Connective and Other Soft Tissues)	10-90
Table 10-30. Analysis of Hodgkin's Disease	10-93
Table 10-31. Analysis of Non-Hodgkin's Lymphoma	10-96
Table 10-32. Analysis of Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	10-98
Table 10-33. Analysis of All Malignant Skin and Systemic Neoplasms.....	10-101
Table 10-34. Analysis of All Skin and Systemic Neoplasms	10-104
Table 10-35. Analysis of PSA (ng/ml) (Continuous)	10-107
Table 10-36. Analysis of PSA (Discrete)	10-110
Table 10-37. Longitudinal Analysis of Malignant Skin Neoplasms	10-114
Table 10-38. Longitudinal Analysis of Malignant Systemic Neoplasms	10-117
Table 10-39. Longitudinal Analysis of Benign Systemic Neoplasms	10-120
Table 10-40. Summary of Group Analysis (Model 1) for Neoplasia Variables (Ranch Hands vs. Comparisons)	10-125
Table 10-41. Summary of Initial Dioxin Analysis (Model 2) for Neoplasia Variables (Ranch Hands Only).....	10-128
Table 10-42. Summary of Categorized Dioxin Analysis (Model 3) for Neoplasia Variables (Ranch Hands vs. Comparisons)	10-130
Table 10-43. Summary of 1987 Dioxin Analysis (Model 4) for Neoplasia Variables (Ranch Hands Only).....	10-133
Table 11-1. Statistical Analysis for the Neurological Assessment.....	11-10
Table 11-2. Number of Participants Excluded or with Missing Data for the Neurological Assessment	11-13
Table 11-3. Analysis of Inflammatory Diseases.....	11-18
Table 11-4. Analysis of Hereditary and Degenerative Diseases	11-21
Table 11-5. Analysis of Peripheral Disorders	11-24
Table 11-6. Analysis of Other Neurological Disorders	11-26
Table 11-7. Analysis of Smell	11-29
Table 11-8. Analysis of Visual Fields	11-32
Table 11-9. Analysis of Light Reaction.....	11-35

Table 11-10. Analysis of Ocular Movement	11-37
Table 11-11. Analysis of Facial Sensation	11-40
Table 11-12. Analysis of Jaw Clench	11-43
Table 11-13. Analysis of Smile	11-46
Table 11-14. Analysis of Palpebral Fissure	11-48
Table 11-15. Analysis of Balance	11-51
Table 11-16. Analysis of Speech	11-54
Table 11-17. Analysis of Tongue Position Relative to Midline	11-56
Table 11-18. Analysis of Palate and Uvula Movement	11-59
Table 11-19. Analysis of Cranial Nerve Index	11-62
Table 11-20. Analysis of Neck Range of Motion	11-64
Table 11-21. Analysis of Pinprick	11-67
Table 11-22. Analysis of Light Touch	11-69
Table 11-23. Analysis of Muscle Status	11-72
Table 11-24. Analysis of Patellar Reflex	11-74
Table 11-25. Analysis of Achilles Reflex	11-77
Table 11-26. Analysis of Biceps Reflex	11-79
Table 11-27. Analysis of Babinski Reflex	11-82
Table 11-28. Analysis of Polyneuropathy Severity Index	11-85
Table 11-29. Analysis of Polyneuropathy Prevalence Index	11-91
Table 11-30. Analysis of Multiple Polyneuropathy Index	11-94
Table 11-31. Analysis of Confirmed Polyneuropathy Indicator	11-97
Table 11-32. Analysis of Tremor	11-100
Table 11-33. Analysis of Coordination	11-102
Table 11-34. Analysis of Romberg Sign	11-104
Table 11-35. Analysis of Gait	11-107
Table 11-36. Analysis of CNS Index	11-109
Table 11-37. Longitudinal Analysis of Cranial Nerve Index	11-112
Table 11-38. Longitudinal Analysis of CNS Index	11-115
Table 11-39. Summary of Group Analysis (Model 1) for Neurology Variables (Ranch Hands vs. Comparisons)	11-119
Table 11-40. Summary of Initial Dioxin Analysis (Model 2) for Neurology Variables (Ranch Hands Only)	11-122

Table 11-41. Summary of Categorized Dioxin Analysis (Model 3) for Neurology Variables (Ranch Hands vs. Comparisons)	11-123
Table 11-42. Summary of 1987 Dioxin Analysis (Model 4) for Neurology Variables (Ranch Hands Only).....	11-126
Table 12-1. Statistical Analysis for the Psychological Assessment	12-7
Table 12-2. Number of Participants Excluded or with Missing Data for the Psychological Assessment.....	12-9
Table 12-3. Analysis of Psychoses	12-15
Table 12-4. Analysis of Alcohol Dependence	12-17
Table 12-5. Analysis of Drug Dependence.....	12-19
Table 12-6. Analysis of Anxiety	12-22
Table 12-7. Analysis of Other Neuroses.....	12-25
Table 12-8. Analysis of SCL-90-R Anxiety	12-28
Table 12-9. Analysis of SCL-90-R Depression	12-31
Table 12-10. Analysis of SCL-90-R Hostility	12-34
Table 12-11. Analysis of SCL-90-R Interpersonal Sensitivity	12-37
Table 12-12. Analysis of SCL-90-R Obsessive-Compulsive Behavior	12-40
Table 12-13. Analysis of SCL-90-R Paranoid Ideation	12-42
Table 12-14. Analysis of SCL-90-R Phobic Anxiety	12-45
Table 12-15. Analysis of SCL-90-R Psychoticism.....	12-48
Table 12-16. Analysis of SCL-90-R Somatization	12-51
Table 12-17. Analysis of SCL-90-R Global Severity Index (GSI).....	12-54
Table 12-18. Analysis of SCL-90-R Positive Symptom Total (PST).....	12-57
Table 12-19. Analysis of SCL-90-R Positive Symptom Distress Index (PSDI).....	12-60
Table 12-20. Summary of Group Analysis (Model 1) for Psychological Variables (Ranch Hands vs. Comparisons)	12-63
Table 12-21. Summary of Initial Dioxin Analysis (Model 2) for Psychological Variables (Ranch Hands Only).....	12-65
Table 12-22. Summary of Categorized Dioxin Analysis (Model 3) for Psychological Variables (Ranch Hands vs. Comparisons)	12-66
Table 12-23. Summary of 1987 Dioxin Analysis (Model 4) for Psychological Variables (Ranch Hands Only).....	12-67
Table 13-1. Statistical Analysis for the Gastrointestinal Assessment	13-6
Table 13-2. Number of Participants Excluded or with Missing Data for the Gastrointestinal Assessment.....	13-10
Table 13-3. Analysis of Uncharacterized Hepatitis.....	13-19

Table 13-4. Analysis of Jaundice (Unspecified)	13-21
Table 13-5. Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-related)	13-24
Table 13-6. Analysis of Chronic Liver Disease and Cirrhosis (Non-alcohol-related)	13-27
Table 13-7. Analysis of Liver Abscess and Sequelae of Chronic Liver Disease	13-29
Table 13-8. Analysis of Enlarged Liver (Hepatomegaly).....	13-32
Table 13-9. Analysis of Other Liver Disorders	13-34
Table 13-10. Analysis of Current Hepatomegaly	13-37
Table 13-11. Analysis of AST (U/l) (Continuous)	13-39
Table 13-12. Analysis of AST (Discrete)	13-42
Table 13-13. Analysis of ALT (U/l) (Continuous)	13-45
Table 13-14. Analysis of ALT (Discrete).....	13-48
Table 13-15. Analysis of GGT (U/l) (Continuous)	13-51
Table 13-16. Analysis of GGT (Discrete)	13-54
Table 13-17. Analysis of Alkaline Phosphatase (U/l) (Continuous)	13-56
Table 13-18. Analysis of Alkaline Phosphatase (Discrete)	13-60
Table 13-19. Analysis of Total Bilirubin (mg/dl) (Continuous)	13-62
Table 13-20. Analysis of Total Bilirubin (Discrete)	13-65
Table 13-21. Analysis of Direct Bilirubin	13-67
Table 13-22. Analysis of Lactic Dehydrogenase (U/l) (Continuous).....	13-69
Table 13-23. Analysis of Lactic Dehydrogenase (Discrete).....	13-72
Table 13-24. Analysis of Cholesterol (mg/dl) (Continuous)	13-74
Table 13-25. Analysis of Cholesterol (Discrete)	13-77
Table 13-26. Analysis of HDL Cholesterol (mg/dl) (Continuous).....	13-80
Table 13-27. Analysis of HDL Cholesterol (Discrete)	13-83
Table 13-28. Analysis of Cholesterol-HDL Ratio (Continuous)	13-85
Table 13-29. Analysis of Cholesterol-HDL Ratio (Discrete)	13-89
Table 13-30. Analysis of Triglycerides (mg/dl) (Continuous)	13-91
Table 13-31. Analysis of Triglycerides (Discrete)	13-94
Table 13-32. Analysis of Creatine Phosphokinase (U/l) (Continuous)	13-97
Table 13-33. Analysis of Creatine Phosphokinase (Discrete)	13-100
Table 13-34. Analysis of Serum Amylase (U/l) (Continuous)	13-102
Table 13-35. Analysis of Serum Amylase (Discrete)	13-106
Table 13-36. Analysis of Antibodies for Hepatitis A	13-108

Table 13-37. Analysis of Evidence of Prior Hepatitis B	13-110
Table 13-38. Analysis of Current Hepatitis B	13-113
Table 13-39. Analysis of Antibodies for Hepatitis C	13-115
Table 13-40. Analysis of Stool Hemoccult.....	13-118
Table 13-41. Analysis of Prealbumin (mg/dl) (Continuous)	13-120
Table 13-42. Analysis of Prealbumin (Discrete)	13-123
Table 13-43. Analysis of Albumin (mg/dl) (Continuous)	13-125
Table 13-44. Analysis of Albumin (Discrete)	13-128
Table 13-45. Analysis of α -1-Acid Glycoprotein (mg/dl) (Continuous).....	13-130
Table 13-46. Analysis of α -1-Acid Glycoprotein (Discrete).....	13-133
Table 13-47. Analysis of α -1-Antitrypsin (mg/dl) (Continuous)	13-136
Table 13-48. Analysis of α -1-Antitrypsin (Discrete)	13-140
Table 13-49. Analysis of α -2-Macroglobulin (mg/dl) (Continuous).....	13-144
Table 13-50. Analysis of α -2-Macroglobulin (Discrete).....	13-147
Table 13-51. Analysis of Apolipoprotein B (mg/dl) (Continuous)	13-150
Table 13-52. Analysis of Apolipoprotein B (Discrete)	13-153
Table 13-53. Analysis of C3 Complement (mg/dl) (Continuous)	13-155
Table 13-54. Analysis of C3 Complement (Discrete)	13-158
Table 13-55. Analysis of C4 Complement (mg/dl) (Continuous)	13-161
Table 13-56. Analysis of C4 Complement (Discrete)	13-164
Table 13-57. Analysis of Haptoglobin (mg/dl) (Continuous)	13-167
Table 13-58. Analysis of Haptoglobin (Discrete).....	13-170
Table 13-59. Analysis of Transferrin (mg/dl) (Continuous)	13-172
Table 13-60. Analysis of Transferrin (Discrete)	13-176
Table 13-61. Normal Ranges from Air Force Health Study Examinations for Dependent Variables Used in Longitudinal Analysis	13-179
Table 13-62. Longitudinal Analysis of AST (U/l) (Continuous)	13-180
Table 13-63. Longitudinal Analysis of AST (Discrete)	13-182
Table 13-64. Longitudinal Analysis of ALT (U/l) (Continuous)	13-185
Table 13-65. Longitudinal Analysis of ALT (Discrete)	13-187
Table 13-66. Longitudinal Analysis of GGT (U/l) (Continuous).....	13-190
Table 13-67. Longitudinal Analysis of GGT (Discrete).....	13-192
Table 13-68. Longitudinal Analysis of Cholesterol (mg/dl) (Continuous)	13-195
Table 13-69. Longitudinal Analysis of Cholesterol (Discrete)	13-197

Table 13-70. Longitudinal Analysis of HDL Cholesterol (mg/dl) (Continuous)	13-200
Table 13-71. Longitudinal Analysis of HDL Cholesterol (Discrete)	13-202
Table 13-72. Longitudinal Analysis of Cholesterol-HDL Ratio (Continuous)	13-205
Table 13-73. Longitudinal Analysis of Cholesterol-HDL Ratio (Discrete)	13-207
Table 13-74. Longitudinal Analysis of Triglycerides (mg/dl) (Continuous)	13-210
Table 13-75. Longitudinal Analysis of Triglycerides (Discrete)	13-212
Table 13-76. Summary of Group Analysis (Model 1) for Gastrointestinal Variables (Ranch Hands vs. Comparisons)	13-217
Table 13-77. Summary of Initial Dioxin Analysis (Model 2) for Gastrointestinal Variables (Ranch Hands Only).....	13-221
Table 13-78. Summary of Categorized Dioxin Analysis (Model 3) for Gastrointestinal Variables (Ranch Hands vs. Comparisons).....	13-224
Table 13-79. Summary of 1987 Dioxin Analysis (Model 4) for Gastrointestinal Variables (Ranch Hands Only).....	13-228
Table 14-1. Statistical Analysis for the Cardiovascular Assessment	14-8
Table 14-2. Number of Participants Excluded or with Missing Data for the Cardiovascular Assessment.....	14-11
Table 14-3. Analysis of Essential Hypertension.....	14-18
Table 14-4. Analysis of Heart Disease (Excluding Essential Hypertension)	14-21
Table 14-5. Analysis of Myocardial Infarction	14-23
Table 14-6. Analysis of Stroke or Transient Ischemic Attack.....	14-26
Table 14-7. Analysis of Systolic Blood Pressure (Continuous)	14-28
Table 14-8. Analysis of Systolic Blood Pressure (Discrete)	14-32
Table 14-9. Analysis of Diastolic Blood Pressure (Continuous).....	14-35
Table 14-10. Analysis of Diastolic Blood Pressure (Discrete).....	14-38
Table 14-11. Analysis of Heart Sounds	14-40
Table 14-12. Analysis of Overall Electrocardiograph (ECG)	14-43
Table 14-13. Analysis of Right Bundle Branch Block	14-45
Table 14-14. Analysis of Left Bundle Branch Block	14-47
Table 14-15. Analysis of Non-Specific ST- and T-Wave Changes	14-50
Table 14-16. Analysis of Bradycardia	14-52
Table 14-17. Analysis of Tachycardia.....	14-55
Table 14-18. Analysis of Arrhythmia	14-58
Table 14-19. Analysis of Evidence of Prior Myocardial Infarction	14-60
Table 14-20. Analysis of ECG: Other Diagnoses	14-63

Table 14-21. Analysis of Funduscopic Examination.....	14-66
Table 14-22. Analysis of Carotid Bruits.....	14-69
Table 14-23. Analysis of Radial Pulses.....	14-71
Table 14-24. Analysis of Femoral Pulses	14-74
Table 14-25. Analysis of Popliteal Pulses	14-76
Table 14-26. Analysis of Dorsalis Pedis Pulses	14-79
Table 14-27. Analysis of Posterior Tibial Pulses	14-81
Table 14-28. Analysis of Leg Pulses	14-83
Table 14-29. Analysis of Peripheral Pulses	14-86
Table 14-30. Analysis of ICVI Index	14-88
Table 14-31. Longitudinal Analysis of Systolic Blood Pressure (mm Hg) (Continuous).....	14-92
Table 14-32. Longitudinal Analysis of Systolic Blood Pressure (Discrete).....	14-95
Table 14-33. Longitudinal Analysis of Femoral Pulses	14-98
Table 14-34. Longitudinal Analysis of Popliteal Pulses	14-101
Table 14-35. Longitudinal Analysis of Dorsalis Pedis Pulses.....	14-103
Table 14-36. Longitudinal Analysis of Posterior Tibial Pulses	14-106
Table 14-37. Longitudinal Analysis of Leg Pulses	14-108
Table 14-38. Longitudinal Analysis of Peripheral Pulses	14-111
Table 14-39. Summary of Group Analysis (Model 1) for Cardiovascular Variables (Ranch Hands vs. Comparisons).....	14-115
Table 14-40. Summary of Initial Dioxin Analysis (Model 2) for Cardiovascular Variables (Ranch Hands Only).....	14-118
Table 14-41. Summary of Categorized Dioxin Analysis (Model 3) for Cardiovascular Variables (Ranch Hands vs. Comparisons).....	14-119
Table 14-42. Summary of 1987 Dioxin Analysis (Model 4) for Cardiovascular Variables (Ranch Hands Only).....	14-121
Table 15-1. Statistical Analysis for the Hematologic Assessment	15-6
Table 15-2. Number of Participants Excluded or with Missing Data for the Hematology Assessment.....	15-8
Table 15-3. Analysis of RBC Count (million/mm ³) (Continuous).....	15-13
Table 15-4. Analysis of RBC Count (Discrete).....	15-16
Table 15-5. Analysis of WBC Count (thousand/mm ³) (Continuous).....	15-20
Table 15-6. Analysis of WBC Count (Discrete).....	15-24
Table 15-7. Analysis of Hemoglobin (gm/dl) (Continuous).....	15-28
Table 15-8. Analysis of Hemoglobin (Discrete).....	15-32

Table 15-9. Analysis of Hematocrit (percent) (Continuous)	15-37
Table 15-10. Analysis of Hematocrit (Discrete).....	15-40
Table 15-11. Analysis of Platelet Count (thousand/mm ³) (Continuous)	15-45
Table 15-12. Analysis of Platelet Count (Discrete).....	15-49
Table 15-13. Analysis of Prothrombin Time (seconds) (Continuous)	15-54
Table 15-14. Analysis of Prothrombin Time (Discrete)	15-57
Table 15-15. Analysis of RBC Morphology	15-59
Table 15-16. Analysis of Absolute Neutrophils (segs) (thousand/mm ³)	15-62
Table 15-17. Analysis of Absolute Neutrophils (bands) (thousand/mm ³) (Nonzero Measurements).....	15-65
Table 15-18. Analysis of Absolute Neutrophils (bands) (Zero vs. Nonzero).....	15-69
Table 15-19. Analysis of Absolute Lymphocytes (thousand/mm ³)	15-71
Table 15-20. Analysis of Absolute Monocytes (thousand/mm ³)	15-75
Table 15-21. Analysis of Absolute Eosinophils (thousand/mm ³) (Nonzero Measurements)	15-78
Table 15-22. Analysis of Absolute Eosinophils (Zero vs. Nonzero).....	15-81
Table 15-23. Analysis of Absolute Basophils (thousand/mm ³) (Nonzero Measurements)	15-84
Table 15-24. Analysis of Absolute Basophils (Zero vs. Nonzero).....	15-87
Table 15-25. Longitudinal Analysis of Platelet Count (thousand/mm ³) (Continuous)	15-91
Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal).....	15-94
Table 15-27. Summary of Group Analysis (Model 1) for Hematology Variables (Ranch Hands vs. Comparisons)	15-101
Table 15-28. Summary of Initial Dioxin Analysis (Model 2) for Hematology Variables (Ranch Hands Only).....	15-104
Table 15-29. Summary of Categorized Dioxin Analysis (Model 3) for Hematology Variables (Ranch Hands vs. Comparisons)	15-106
Table 15-30. Summary of 1987 Dioxin Analysis (Model 4) for Hematology Variables (Ranch Hands Only).....	15-109
Table 16-1. Statistical Analysis for the Endocrine Assessment	16-8
Table 16-2. Number of Participants Excluded or with Missing Data for the Endocrine Assessment	16-11
Table 16-3. Analysis of Past Thyroid Disease.....	16-16
Table 16-4. Analysis of Composite Diabetes Indicator	16-19
Table 16-5. Analysis of Diabetic Severity	16-23
Table 16-6. Analysis of Time to Diabetes Onset (years).....	16-29
Table 16-7. Analysis of Thyroid Gland	16-32

Table 16-8. Analysis of Testicular Examination	16-35
Table 16-9. Analysis of TSH (μ IU/ml) (Continuous)	16-37
Table 16-10. Analysis of TSH (Discrete)	16-41
Table 16-11. Analysis of Thyroxine (μ g/dl) (Continuous).....	16-46
Table 16-12. Analysis of Thyroxine (Discrete).....	16-49
Table 16-13. Analysis of Anti-Thyroid Antibodies.....	16-51
Table 16-14. Analysis of Fasting Glucose (mg/dl) (Continuous).....	16-54
Table 16-15. Analysis of Fasting Glucose (Discrete).....	16-57
Table 16-16. Analysis of 2-Hour Postprandial Glucose (mg/dl) (Continuous).....	16-60
Table 16-17. Analysis of 2-Hour Postprandial Glucose (Discrete).....	16-63
Table 16-18. Analysis of Fasting Urinary Glucose	16-65
Table 16-19. Analysis of 2-Hour Postprandial Urinary Glucose	16-68
Table 16-20. Analysis of Serum Insulin (μ IU/ml) (Continuous).....	16-71
Table 16-21. Analysis of Serum Insulin (Discrete)	16-75
Table 16-22. Analysis of α -1-C Hemoglobin (percent) (Continuous)	16-80
Table 16-23. Analysis of α -1-C Hemoglobin (Discrete)	16-83
Table 16-24. Analysis of Total Testosterone (ng/dl) (Continuous)	16-86
Table 16-25. Analysis of Total Testosterone (Discrete)	16-89
Table 16-26. Analysis of Free Testosterone (pg/ml) (Continuous)	16-92
Table 16-27. Analysis of Free Testosterone (Discrete)	16-95
Table 16-28. Analysis of Estradiol (pg/ml) (Continuous)	16-97
Table 16-29. Analysis of Estradiol (Discrete)	16-100
Table 16-30. Analysis of LH (mIU/ml) (Continuous).....	16-103
Table 16-31. Analysis of LH (Discrete)	16-106
Table 16-32. Analysis of FSH (mIU/ml) (Continuous)	16-108
Table 16-33. Analysis of FSH (Discrete)	16-112
Table 16-34. Normal Ranges from Air Force Health Study Examinations for Dependent Variables Used in Endocrine Longitudinal Analysis	16-115
Table 16-35. Longitudinal Analysis of Composite Diabetes Indicator	16-115
Table 16-36. Longitudinal Analysis of TSH (μ IU/ml) (Continuous).....	16-118
Table 16-37. Longitudinal Analysis of TSH (Discrete)	16-120
Table 16-38. Longitudinal Analysis of Fasting Glucose (mg/dl) (Continuous).....	16-122
Table 16-39. Longitudinal Analysis of Fasting Glucose (Discrete)	16-125
Table 16-40. Longitudinal Analysis of 2-Hour Postprandial Glucose (mg/dl) (Continuous)	16-128

Table 16-41. Longitudinal Analysis of 2-Hour Postprandial Glucose (Discrete)	16-131
Table 16-42. Longitudinal Analysis of Total Testosterone (ng/dl) (Continuous).....	16-134
Table 16-43. Longitudinal Analysis of Total Testosterone (Discrete).....	16-137
Table 16-44. Summary of Group Analysis (Model 1) for Endocrine Variables (Ranch Hands vs. Comparisons)	16-141
Table 16-45. Summary of Initial Dioxin Analysis (Model 2) for Endocrine Variables (Ranch Hands Only).....	16-144
Table 16-46. Summary of Categorized Dioxin Analysis (Model 3) for Endocrine Variables (Ranch Hands vs. Comparisons)	16-146
Table 16-47. Summary of 1987 Dioxin Analysis (Model 4) for Endocrine Variables (Ranch Hands Only).....	16-148
Table 17-1. Medical Significance of the Immunologic Data.....	17-6
Table 17-2. Statistical Analysis for the Immunologic Assessment	17-10
Table 17-3. Number of Participants Excluded or with Missing Data for the Immunologic Assessment	17-12
Table 17-4. Analysis of CD3+ Cells (T Cells) (cells/mm ³).....	17-17
Table 17-5. Analysis of CD4+ Cells (Helper T Cells) (cells/mm ³).....	17-21
Table 17-6. Analysis of CD8+ Cells (Suppressor T Cells) (cells/mm ³).....	17-23
Table 17-7. Analysis of CD16+56+ Cells (Natural Killer Cells) (cells/mm ³)	17-27
Table 17-8. Analysis of CD20+ Cells (B Cells) (cells/mm ³)	17-30
Table 17-9. Analysis of CD3+CD4+ Cells (Helper T Cells) (cells/mm ³)	17-33
Table 17-10. Analysis of Absolute Lymphocytes (cells/mm ³)	17-35
Table 17-11. Analysis of IgA (mg/dl).....	17-38
Table 17-12. Analysis of IgG (mg/dl).....	17-41
Table 17-13. Analysis of IgM (mg/dl)	17-44
Table 17-14. Analysis of Lupus Panel: ANA Test	17-47
Table 17-15. Analysis of Lupus Panel: ANA Thyroid Microsomal Antibody.....	17-49
Table 17-16. Analysis of Lupus Panel: MSK Smooth Muscle Antibody.....	17-52
Table 17-17. Analysis of Lupus Panel: MSK Mitochondrial Antibody	17-54
Table 17-18. Analysis of Lupus Panel: MSK Parietal Antibody	17-58
Table 17-19. Analysis of Lupus Panel: Rheumatoid Factor	17-60
Table 17-20. Summary of Group Analysis (Model 1) for Immunology Variables (Ranch Hands vs. Comparisons)	17-67
Table 17-21. Summary of Initial Dioxin Analysis (Model 2) for Immunology Variables (Ranch Hands Only).....	17-69

Table 17-22. Summary of Categorized Dioxin Analysis (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)	17-70
Table 17-23. Summary of 1987 Dioxin Analysis (Model 4) for Immunology Variables (Ranch Hands Only).....	17-72
Table 18-1. Statistical Analysis for the Pulmonary Assessment	18-6
Table 18-2. Number of Participants Excluded or with Missing Data for the Pulmonary Assessment.....	18-8
Table 18-3. Analysis of Asthma	18-12
Table 18-4. Analysis of Bronchitis.....	18-14
Table 18-5. Analysis of Pneumonia.....	18-17
Table 18-6. Analysis of Thorax and Lung Abnormalities	18-19
Table 18-7. Analysis of X-ray Interpretation.....	18-22
Table 18-8. Analysis of FVC (Percent of Predicted).....	18-25
Table 18-9. Analysis of FEV ₁ (Percent of Predicted).....	18-27
Table 18-10. Analysis of the Ratio of Observed FEV ₁ to Observed FVC	18-30
Table 18-11. Analysis of Loss of Vital Capacity	18-33
Table 18-12. Analysis of Obstructive Abnormality.....	18-37
Table 18-13. Longitudinal Analysis of the Ratio of Observed FEV ₁ to Observed FVC	18-42
Table 18-14. Summary of Group Analysis (Model 1) for Pulmonary Variables (Ranch Hands vs. Comparisons)	18-47
Table 18-15. Summary of Initial Dioxin Analysis (Model 2) for Pulmonary Variables (Ranch Hands Only).....	18-48
Table 18-16. Summary of Categorized Dioxin Analysis (Model 3) for Pulmonary Variables (Ranch Hands vs. Comparisons)	18-50
Table 18-17. Summary of 1987 Dioxin Analysis (Model 4) for Pulmonary Variables (Ranch Hands Only).....	18-52

List of Figures

Figure 2-1.	Decision Process for Determination of Dioxin Results for Analysis.....	2-4
Figure 2-2.	Relative Frequency Distribution of Lipid-adjusted Dioxin Concentrations for 863 Ranch Hands	2-7
Figure 2-3.	Relative Frequency Distribution of Lipid-adjusted Dioxin Concentrations for 1,232 Comparisons.....	2-7
Figure 2-4.	Relative Frequency Distribution of Lipid-adjusted Dioxin Concentrations	2-8
Figure 2-5.	Relative Frequency Distribution of the Logarithm (Base 2) of Lipid- adjusted Dioxin Concentrations.....	2-8
Figure 4-1.	Typical 2-Day Clinic Schedule	4-6
Figure 5-1.	Cumulative Percent Completed Physical Examination by Calendar Date	5-5
Figure 6-1.	Participant Evaluations of the 1997 AFHS Clinic Experience	6-5
Figure 6-2.	Physical Examination Form QC Process.....	6-8
Figure 6-3.	Conversion and Cleaning Process for Medical Data.....	6-10

EXECUTIVE SUMMARY – 1997 FOLLOW-UP EXAMINATION REPORT

The Air Force Health Study (AFHS) is an epidemiological investigation to determine whether adverse health effects exist in Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971, and whether these adverse health effects can be attributed to occupational exposure to Herbicide Orange (or its dioxin contaminant). A comparison group was formed from Air Force veterans who flew or maintained C-130 aircraft in Southeast Asia (SEA) during the same time period as those who served in the Ranch Hand units and who were not involved with spraying herbicides. The baseline study was conducted in 1982; follow-up studies were performed in 1985, 1987, 1992, and 1997. Participation was voluntary, and consent forms were signed by the participant at the examination site. An additional evaluation is planned for 2002. This report presents the results from the statistical analyses of the data from the 1997 follow-up examination.

In the baseline study, each living Ranch Hand was matched with a randomly selected Comparison based on age, race, and military occupation. At each follow-up study, noncompliant Comparisons were replaced from the set of living Comparisons, matched by age, race, military occupation, and self-perception of health. A total of 2,121 veterans participated in the 1997 follow-up examination. Of the 1,101 eligible Ranch Hands, 870 (79.0%) participated in the 1997 follow-up examination. A total of 839 of the 1,151 eligible Original Comparisons (72.9%) participated. Of the 768 eligible Replacement Comparisons, 412 (53.6%) chose to attend the examination. A total of 1,251 Comparisons attended the 1997 follow-up examination. Eighty-six percent (819 of 949) of living Ranch Hands and 87 percent of living Comparisons (976 of 1,116) who were fully compliant at the baseline examination returned for the 1997 follow-up examination.

This report presents conclusions drawn from the statistical analyses of 266 health-related endpoints in 10 clinical areas: general health, neoplasia, neurology, psychology, gastrointestinal, cardiovascular, hematology, endocrine, immunology, and pulmonary. Analysis was not performed on nine of these endpoints because of a sparse number of abnormalities. Data were collected from a medical records review, previous examinations, and the physical and laboratory examinations and questionnaire administered at the 1997 follow-up examination. The analyses focused on group differences between the exposed (Ranch Hand) and unexposed (Comparison) cohorts, as well as on the association between serum dioxin levels and each health-related endpoint among the Ranch Hands.

Four statistical models were used to evaluate the relation between the health status of study participants and their herbicide or dioxin exposure. The first model (Model 1) examines contrasts between Ranch Hands and Comparisons using group as a proxy for herbicide exposure and does not incorporate serum dioxin measurements. However, it is assumed in this model that all Ranch Hands were exposed and all Comparisons were not exposed to herbicides. Each of the following three models incorporates estimates of serum dioxin in either initial or current form. Current serum dioxin was based on measurements from the 1987 examination. When a 1987 dioxin measurement was not available, measurements from the 1992 or 1997 examinations were used to supplement the 1987 measurement. Initial serum dioxin was extrapolated from the current serum dioxin measurement to time of duty in SEA. The second model (Model 2) examines estimated initial serum dioxin levels, extrapolated from current serum dioxin measurements and assuming first-order kinetics and a constant dioxin elimination rate. The third model (Model 3) categorizes the Ranch Hand cohort according to serum dioxin levels and contrasts each Ranch Hand category with the Comparisons having background serum dioxin levels. The fourth model (Model 4) uses a 1987 lipid-adjusted measure of serum dioxin. This model requires no assumptions about serum dioxin elimination. The extrapolated initial dose and lipid-adjusted dioxin measurements in Models 2, 3, and 4 may not be good measures of exposure if elimination rates differ among individuals.

In the general health assessment, the self-perception of health analysis revealed significant differences between Ranch Hands and Comparisons, with more Ranch Hands than Comparisons indicating their health as fair or poor. As in previous examinations, the difference was most apparent in enlisted groundcrew, who had the highest average dioxin levels. This observation also was confirmed in the categorized dioxin analysis, where Ranch Hands with the highest dioxin levels perceived their health as fair or poor more often than Comparisons. Also, among Ranch Hands, those with the higher 1987 dioxin levels reported fair or poor health more often than Ranch Hands with lower levels. These results were consistent with the 1985, 1987, and 1992 examinations. No group differences were noted in the appearance of illness or relative age, as recorded by examining physicians, nor were these variables correlated with serum dioxin levels in the Ranch Hand cohort. The analysis of body fat indicated positive associations with dioxin levels. The results of the 1997 examination confirmed those of the 1992 examination and appear consistent with a difference in dioxin pharmacokinetics in obese versus lean individuals. No differences in either the risk of an abnormal erythrocyte sedimentation rate between Ranch Hands and Comparisons or the relations between abnormal erythrocyte sedimentation rates and dioxin levels were observed during the 1997 examination. Erythrocyte sedimentation rates increased as 1987 dioxin levels increased. Longitudinal analyses showed that Ranch Hands, particularly the enlisted personnel, had a greater percentage of abnormal erythrocyte sedimentation rates than did Comparisons during the 15 years of the study since 1982. These analyses also showed that the percentages of abnormalities increased from 1982 to 1997 as dioxin levels increased. This result was seen at the 1987 study, but not in 1992. This positive association raises the possibility of a subtle inflammatory, infectious, or occult malignant disease process related to the body burden of dioxin. In conclusion, fair or poor self-perception of health displayed an adverse association with dioxin. Increased body fat was associated with increased levels of dioxin, a finding most likely related to the pharmacokinetics of dioxin. Longitudinal analyses indicated an increased risk of abnormal erythrocyte sedimentation rates in Ranch Hands over Comparisons in the 15 years of the AFHS, and a relation between abnormal erythrocyte sedimentation rates and levels of dioxin during these 15 years. Other measures of general health revealed no association with levels of dioxin.

In the assessment of malignant neoplastic disease, at the end of 15 years of surveillance, Ranch Hands as a group exhibited a nonsignificant increase in the risk of malignant neoplastic disease relative to Comparisons (relative risk=1.06, 95% confidence interval: [0.80,1.41]). Military occupation contrasts were inconsistent and, therefore, not supportive of an adverse effect of herbicide or dioxin exposure on the occurrence of malignancies. Ranch Hand enlisted groundcrew, the occupation with the highest dioxin levels and, presumably, the highest herbicide exposure, exhibited a decreased prevalence (relative risk=0.78, 95% confidence interval: [0.51,1.19]). Enlisted flyers (relative risk=1.63, 95% confidence interval: [0.91,2.92]) and officers (relative risk=1.14, 95% confidence interval: [0.79,1.65]), occupations with lower dioxin levels, exhibited nonsignificant increases in the prevalence of malignant disease. The risk of malignant disease was nonsignificantly increased among Ranch Hands having the highest dioxin levels (relative risk=1.01, 95% confidence interval: [0.66,1.57]). Longitudinal analyses found no significant group differences with regard to the risk of malignancy and no pattern suggestive of an adverse relation between herbicide or dioxin exposure and the occurrence of malignant neoplastic disease.

In the neurological assessment, four neurological disorders and extensive physical examination data on cranial nerve function, peripheral nerve status, and central nervous system coordination processes were analyzed. Inflammatory diseases, as verified by a medical records review, were increased in Ranch Hands relative to Comparisons in terms of both a group designation and categorized dioxin levels. Peripheral disorders, as verified by a medical records review, increased in Ranch Hands as levels of 1987 dioxin increased. Neck range of motion abnormalities were increased in Ranch Hands relative to Comparisons in terms of both a group designation and categorized dioxin levels. The increase in

abnormalities for Ranch Hands relative to Comparisons was noted in enlisted flyers. An increase in the risk of an abnormal muscle status was observed in Ranch Hand enlisted groundcrew. A significant association between initial dioxin and abnormalities of both visual fields and the patellar reflex was observed. Indices of polyneuropathy showed an increase in the prevalence of abnormality in Ranch Hands relative to Comparisons and a positive association with initial dioxin, categorized dioxin, and 1987 dioxin levels. In summary, although a common etiology in these findings is not apparent, a statistically significant increase in neurological disease appears in Ranch Hands historically, on physical examination, and as reflected in several of the composite polyneuropathy indices. Further, the associations of abnormal neck range of motion with categorized dioxin and a history of peripheral disorders with 1987 dioxin provide evidence of an association of neurological disease with elevated dioxin levels. The results of the analysis of the polyneuropathy indices also provide support of a statistical association between elevated dioxin levels and neurological disease; however, the clinical importance of this finding is uncertain.

Five psychological disorders, which were verified by a medical records review, and 12 measures from the Symptom Checklist-90-Revised (SCL-90-R) inventory were examined in the psychology assessment. The SCL-90-R consisted of nine primary symptom dimensions and three broad indices of psychological distress. In enlisted groundcrew a significantly greater percentage of Ranch Hands than Comparisons had a history of other neuroses. All other significant results from analyses of Ranch Hands versus Comparisons showed a greater percentage of Comparisons than Ranch Hands with high SCL-90-R scores. Associations between initial dioxin and the psychological endpoints were either nonsignificant or revealed a significant decrease in high SCL-90-R scores as initial dioxin increased. Differences in the history of psychological disorders and the prevalence of high SCL-90-R scores were examined between Comparisons and Ranch Hands categorized by dioxin levels. Ranch Hands in the low dioxin category and the low plus high dioxin category displayed a significantly higher occurrence of other neuroses than did Comparisons. The relation between the 1987 dioxin levels and the psychological endpoints was examined and all results were nonsignificant. In summary, Ranch Hand veterans exhibited a significantly increased prevalence of other neuroses among enlisted groundcrew, the military occupation with the highest dioxin levels and, presumably, the greatest herbicide exposure. Consistent increases in the prevalence of other neuroses with dioxin levels were found. No consistent relation was found between any SCL-90-R score and any measure of herbicide or dioxin exposure. The relation between other neuroses and herbicide exposure and dioxin levels will be described in greater detail in a separate report.

The gastrointestinal assessment was based on eight disorders as determined from a review and verification of each participant's medical records, a physical examination determination of hepatomegaly, and 29 laboratory measurements or indices. The laboratory parameters included measurements of hepatic enzyme activity, hepatobiliary function, lipid and carbohydrate indices, and a protein profile. In addition, the presence of hepatitis and fecal occult blood was investigated. Analyses of Ranch Hands versus Comparisons showed higher mean levels of alkaline phosphatase, α -1-antitrypsin, and haptoglobin in Ranch Hands than in Comparisons. In addition, significantly more Ranch Hands than Comparisons had high haptoglobin levels. A review of medical records showed a positive association between initial dioxin and other liver disorders. The other liver disorders condition consisted primarily of nonspecific laboratory test elevations. A significant association between initial dioxin and high levels of aspartate aminotransferase (AST) also was revealed. Analyses of categorized dioxin revealed a significantly higher percentage of other liver disorders among Ranch Hands in the high dioxin category than among Comparisons. Higher mean levels of gamma glutamyl transferase (GGT), triglycerides, and α -1-antitrypsin were observed in Ranch Hands in the high dioxin category than in Comparisons. Ranch Hands in the high dioxin category had a greater prevalence of abnormal AST, triglyceride, and prealbumin levels than did Comparisons. Many significant associations between the laboratory

examination variables and 1987 dioxin levels were observed. In both the continuous and discrete forms, the hepatic enzymes alanine aminotransferase (ALT), AST, and GGT revealed significant, positive associations with 1987 dioxin. In addition, significant positive associations between 1987 dioxin and the ratio of cholesterol to high-density lipoprotein (HDL), triglycerides, and creatine phosphokinase were present. In summary, the analysis of the 1997 follow-up data reflected patterns that have been observed and documented in prior examinations. Isolated group differences exist, but 1987 dioxin levels are strongly related to hepatic enzymes such as AST, ALT, and GGT, and to lipid-related health indices such as cholesterol, HDL, and triglycerides. These results are consistent with a dose-response effect and may be related to unknown subclinical effects of dioxin. Although hepatic enzymes and lipid-related indices showed an association with dioxin, there was no evidence of an increase in overt liver disease.

In the cardiovascular assessment, analyses revealed that Ranch Hands had a significantly higher percentage of participants with a history of heart disease (excluding essential hypertension) than Comparisons and in particular, among enlisted flyers. However, the risk of disease was not significantly increased in Ranch Hand enlisted groundcrew, the military occupation with the highest dioxin levels. The association between heart disease and initial dioxin showed a negative dose-response trend, with heart disease decreasing as initial dioxin increased. Furthermore, Ranch Hands in the background and low dioxin categories had more heart disease than did Comparisons, but this increase was not seen in Ranch Hands in the high dioxin category. Increases in tachycardia and other electrocardiograph (ECG) findings, such as pre-excitation, were seen for Ranch Hands in the high dioxin category, although the analyses were based on a small number of abnormalities. A significant positive association between initial dioxin and evidence of prior myocardial infarction from the ECG was observed in Ranch Hands, and a marginally significant positive association was observed between 1987 dioxin and evidence of prior myocardial infarction from the ECG. A positive association between 1987 dioxin and a history of essential hypertension also was observed in Ranch Hands. In contrast to previous AFHS examinations, no relation was found between peripheral pulse abnormalities and any measure of exposure. In summary the current study has documented that Ranch Hands are more likely than Comparisons to have historical evidence for heart disease (excluding essential hypertension) but are no longer at greater risk for the occurrence of pulse deficits. By all other indices, the prevalence of cardiovascular disease appears similar in both cohorts. For the first time, there is evidence that levels of dioxin may be a risk factor for the development of essential hypertension and prior myocardial infarction as indicated by interpretation of the ECG. As of 1997, the verified history of essential hypertension was associated with 1987 dioxin, and the evidence of prior myocardial infarction from the ECG was associated with initial dioxin. These findings, in conjunction with the increase in the number of deaths caused by diseases of the circulatory system for Ranch Hand nonflying enlisted personnel based on the 1994 AFHS mortality update, showed associations that require further study. A biological mechanism for the relation among dioxin levels and heart disease is unknown.

In the hematologic assessment, five cell count measures, six measures of absolute blood counts, a coagulation measure, and red blood cell morphology were analyzed. In the analyses of these variables, only platelet count exhibited significant dose-response associations with the levels of dioxin. Among enlisted personnel, Ranch Hands exhibited significantly higher mean platelet counts than did Comparisons. Ranch Hands in the high dioxin category also exhibited a significantly higher mean platelet count than did Comparisons. The mean differences were small and, therefore, the clinical importance of these findings is unknown. The results in the 1997 follow-up study parallel the findings of the 1987 and 1992 follow-up studies. In conclusion, apart from platelet count, there appears to be little evidence to support a relation between prior dioxin exposure and hematopoietic toxicity.

The assessment of the endocrine system yielded an extensive evaluation of thyroid, pancreatic, and gonadal function and their relation to dioxin exposure. A significantly increased risk of abnormally high

thyroid stimulating hormone values was found in Ranch Hand enlisted groundcrew. A positive association between diabetes and initial and 1987 dioxin was observed. Consistent with previous reports, the prevalence of diabetes among Ranch Hands with high dioxin levels was significantly increased. A greater percentage of Ranch Hands than Comparisons used insulin to control their type 2 diabetes, primarily among officers and enlisted groundcrew. The percentage of Ranch Hands requiring insulin to control their type 2 diabetes increased with initial dioxin. A greater percentage of Ranch Hands in the high dioxin category required insulin to control their type 2 diabetes than did Comparisons. The percentage of Ranch Hands who treated their diabetes through diet only and the percentage who used oral hypoglycemics increased with 1987 dioxin level. The time to diabetes onset was significantly shorter for Ranch Hands with higher initial dioxin and 1987 levels. Both fasting glucose and α -1-C hemoglobin increased as initial dioxin and 1987 dioxin increased. Increased mean α -1-C hemoglobin levels also were observed for Ranch Hands with high dioxin levels. The presence of fasting urinary glucose also increased with 1987 dioxin. Although cause and effect have not been established, the results cited above provide further evidence for an association between glucose intolerance and levels of dioxin.

The immunologic assessment was based on laboratory data on six lymphocyte cell surface markers, absolute lymphocyte counts, three quantitative immunoglobulins, and six measurements from an autoantibody panel. The six cell marker measurements were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of the tests. Group analyses revealed significant findings for the analyses of CD16+56+ cell (natural killer cell) counts and for the mouse stomach kidney (MSK) smooth muscle antibody test in enlisted flyers. Among enlisted flyers, the mean CD16+56+ cell count was greater for Comparisons than for Ranch Hands, and a greater percentage of Comparisons than Ranch Hands had a smooth muscle antibody present. Negative smooth muscle and mitochondrial antibody tests are considered to be normal. For these analyses, the magnitude of the mean differences was small and, therefore, the clinical importance of these findings is unknown. Consistent with the previous two physical examinations, IgA increased significantly with initial dioxin, but was not significantly increased in enlisted groundcrew or the high dioxin category, and IgA did not increase significantly with 1987 dioxin. The IgA results, although significant, were small in magnitude and their clinical importance is unknown. When comparing categorized dioxin levels between Ranch Hands and Comparisons, a significantly higher CD16+56+ cell count mean was observed among Comparisons than among Ranch Hands in the high dioxin category. Analyses revealed significant associations between 1987 dioxin levels and CD3+ cell (T cell) count, CD4+ cell (helper T cell) count, and CD3+CD4+ cell (helper T cell) count. The cell counts increased as 1987 dioxin increased. In summary, these findings and the findings from past examinations do not provide evidence of a biologically meaningful dose-response effect for body burden of dioxin on parameters of immunologic assessment. The statistically significant relations suggest the need for continued evaluation.

To assess pulmonary status, verified histories of asthma, bronchitis, and pneumonia were studied. A composite measure of thorax and lung abnormalities, as determined from the presence of asymmetrical expansion, hyperresonance, dullness, wheezes, rales, chronic obstructive pulmonary diseases, or the physician's assessment of abnormality, also was analyzed. A routine chest x ray and five measures of pulmonary function using standard spirometric techniques were analyzed. Few significant increases in adverse pulmonary conditions were observed for Ranch Hands, and isolated and inconsistent associations between the pulmonary endpoints and dioxin were seen. No consistent pattern or dose-response relation was evident. Ranch Hands in the background dioxin category exhibited a significantly higher percentage of abnormalities on the chest x ray than did Comparisons. Ranch Hand officers had a significantly higher prevalence of mild obstructive abnormality than did Comparison officers; the corresponding contrast was not significant in 1992, and officers were not analyzed as a separate stratum in 1982, 1985 or 1987. The

relation between mild obstructive abnormality in Ranch Hand officers and other indicators of herbicide exposure, such as job (pilot, navigator, nonflyer), the number of missions flown, the percentage of missions that were herbicide missions, and reported drinking of herbicide (yes, no) will be summarized in a separate report. In summary, analysis of historical, physical examination, and laboratory data revealed no consistent relation between herbicide exposure or dioxin levels and pulmonary disease. The prevalence of mild obstructive abnormalities was significantly increased in Ranch Hand officers. The meaning of this finding is unclear because the risk was not significantly increased in Ranch Hand enlisted groundcrew—the military occupation with the highest dioxin levels.

Certain facts should be considered when drawing conclusions from the statistical analysis of the 1997 follow-up examination results. First, the Ranch Hand and Comparison veterans were not blinded to group membership. In addition, there are often difficulties associated with multiple testing. With repeated statistical testing, the likelihood of a test indicating some artifactual association is high. But longitudinal comparisons of previous examinations may show a consistent association, supporting a non-artifactual relation. Longitudinal tests, however, of the same population clearly are not independent tests. If a chance association was present at the first physical examination, it would tend to persist in subsequent examinations. Conversely, depending on site and mode of action, the association would be expected to increase with time (if latency or other chronic effects predominate) or decrease with time (if the current dioxin level predominates in the mechanism). It is also important to note that some conditions do not appear with reasonable frequency until middle age or later. Therefore, in the early years of the study an increased relative risk might have been masked by abnormalities too sparse for meaningful analysis.

The report recognizes two major limitations to the study. First, the results cannot be generalized to other groups (such as all Vietnam veterans or Vietnamese civilians) who have been exposed in different ways and to different levels of herbicide. We do not know what effect herbicides or dioxin have at levels other than those found in our study group, or from other sources such as contaminated food. Groups with higher exposures may well have effects not seen in our study. Second, the size of the study makes it difficult to detect increases in rare diseases, so small increases of these diseases may be missed by the study. For example, since liver cancer is very rare, even a tenfold increase may not be detected.

The site and mode of action of dioxin in the body could itself either cause or obscure a relation. Receptors might be activated only after a certain dioxin threshold value had been exceeded—that is, a value exceeding the body's capability to safely store dioxin. If, on the other hand, dioxin caused a competitive inhibition of receptor actions normally stimulated by other substances, there might be a "no-threshold" effect. Depending on the nature (lipid or non-lipid) and type of function of the hypothetical receptor site, an increase in body fat over time might either cause an increase in dioxin effect because of a greater volume of distribution or a decrease in dioxin effect because of a lesser concentration at the receptor site.

Strength of association is also an issue in a study of a population this size. A study with a population of 2,121 lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma) because such events are unlikely to occur in large numbers in a group this small. While certain occupational toxins have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually nonexistent in the absence of the toxin, other toxins merely increase the risk of nondiagnostic pathology. For example, this study would likely not discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology. By assessing the pathology observed in association with other known environmental risk factors (e.g., tobacco use, alcohol use) it is sometimes possible to provide a limit in the magnitude of effect missed; however, this study has inherent bounds in detecting modest increases in relative risk for infrequent pathology.

A final difficulty is the presence of a true association that is noncausal. An example might be a condition not caused by dioxin, but resulting in or from an altered dioxin half-life. In this case, a correlation might be high in the total absence of causality.

Clearly, there are many issues to be considered in interpreting these results. With these issues in mind, certain assessments were made by looking at a number of factors. Among these factors are longitudinal trends, biological plausibility, consistency with animal toxicology, the presence of a dose-response relation, and strength of association. But, meeting all of these criteria would not guarantee causality, nor would failing these criteria guarantee the lack of an effect. It can be argued, however, that the good faith application of these particular methods should be the starting point for generating hypotheses for experimental examination through *in vitro* and *in vivo* testing, as well as through further epidemiological analysis of these and other exposed groups.

Based on the findings of the 1997 examination, and subject to the qualifications considered above, the study investigators have drawn the following conclusions.

1. **Diabetes:** Consistent with previously reported results, current data indicate a significant and potentially meaningful adverse relation between serum dioxin levels and diabetes. A significant dose-response was found, with Ranch Hands in the high dioxin category exhibiting an increase in disease prevalence (relative risk=1.47, 95% confidence interval: [1.00,2.17]). The finding is supported by a dioxin-related increase in disease severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and α -1-C hemoglobin. Similar patterns were observed in 1987 and 1992.
2. **Cardiovascular Abnormalities:** Cardiovascular findings are mixed, but, in context with the increased cardiovascular mortality in nonflying enlisted Ranch Hands, are suggestive of an adverse effect of herbicide and dioxin exposure. As a group, Ranch Hands have experienced a statistically significant increase in the prevalence of heart disease (excluding essential hypertension) (relative risk=1.26, 95% confidence interval: [1.05,1.51]). The increase was more than doubled among enlisted flyers (relative risk=2.10, 95% confidence interval: [1.27,3.28]), but not significantly increased among enlisted groundcrew (relative risk=1.10, 95% confidence interval: [0.84,1.42])—the military occupation with the highest dioxin levels. The prevalence of diagnosed essential hypertension and the percentage of Ranch Hands with ECG findings of prior myocardial infarction increased significantly with initial dioxin. Peripheral pulse abnormalities increased with dioxin levels in 1987 and 1992, but did not increase with dioxin levels in 1997. These findings, together with increased cardiovascular mortality in Ranch Hand nonflying enlisted personnel, suggest that herbicide or dioxin exposure may be related to cardiovascular abnormalities.
3. **Peripheral Polyneuropathy:** Although a common etiology is not apparent, a statistically significant increase in neurological disease appears in Ranch Hands historically, on physical examination, and as reflected in several of the composite polyneuropathy indices. Peripheral disorders, as verified by a medical records review, increased in Ranch Hands as levels of 1987 dioxin increased. Indices of bilateral peripheral polyneuropathy, confirmed by vibrotactile measurements in the feet, significantly increased with initial dioxin level, were significantly increased in the high dioxin category, and significantly increased with 1987 dioxin. These findings are new and appear consistent with polyneuropathies observed in studies of industrial exposure; however, the numbers of affected veterans are small and the clinical importance of the findings are uncertain.

4. **Serum Lipid Abnormalities:** There were consistent and significant increases in cholesterol, triglycerides, and the cholesterol-HDL ratio with initial and 1987 dioxin. HDL decreased significantly as dioxin increased. These findings also were observed in 1987 and 1992.
5. **Liver Enzymes:** Analysis of liver function reflected patterns that have been observed in prior examinations. Isolated group differences existed, but 1987 dioxin levels were strongly related to increases in hepatic enzymes such as AST, ALT, and GGT and, as previously noted, cholesterol, triglycerides, and HDL. These results were consistent with an adverse dose-response and may be related to subclinical effects of unknown importance. Although hepatic enzymes increased with dioxin, there is no evidence of a corresponding increase in overt liver disease.
6. **Malignant Neoplastic Disease:** At the end of 15 years of surveillance, Ranch Hands as a group exhibited a nonsignificant increase in the risk of malignant neoplastic disease relative to Comparisons (relative risk=1.06, 95% confidence interval: [0.80,1.41]). Military occupation contrasts were inconsistent and, therefore, not supportive of an adverse effect of herbicide or dioxin exposure on the occurrence of malignancies. Ranch Hand enlisted groundcrew, the occupation with the highest dioxin levels and, presumably, the highest herbicide exposure, exhibited a decreased prevalence (relative risk=0.78, 95% confidence interval: [0.51,1.19]). Enlisted flyers (relative risk=1.63, 95% confidence interval: [0.91,2.92]) and officers (relative risk=1.14, 95% confidence interval: [0.79,1.65]), occupations with lower dioxin levels, exhibited nonsignificant increases in the prevalence of malignant disease. The risk of malignant disease was nonsignificantly increased among Ranch Hands having the highest dioxin levels (relative risk=1.01, 95% confidence interval: [0.66,1.57]). Longitudinal analyses found no significant group differences with regard to the risk of malignancy and no pattern suggestive of an adverse relation between herbicide or dioxin exposure and the occurrence of malignant neoplastic disease.

In conclusion, diabetes and cardiovascular abnormalities represent the most important dioxin-related health problems seen in the AFHS. These two areas appear to have the greatest magnitude of effect in terms of quality of life and healthcare costs. Clearly, there are biological interrelations among both of these outcomes that make interpretations difficult. From a public health perspective, these two areas demand the greatest attention.

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